SEP 10 1900

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL.

Vol. XI.—No. 114.] BALTIMORE, SEPTEMBER, 1900. [Price, 30 Cents.

CONTENTS.

	PAGE
Morbid Conditions Caused by Bacillus Aërogenes Capsulatus. By William H. Welch, M. D.,	185
On the Histology of the Islands of Langerhans of the Pancreas. By Eugene L. Opie, M. D.,	205
The Distribution of Connective Tissue in New Growths. By W. C. White, M. B.,	209
On the Relation of the Electrical Conductivity of Blood-serum to its Alleged Bactericidal Power. By Emma Lootz and Alice Weld Tallant,	220
A Contribution to the Study of Malignant Tumors Arising in Congenital Moles. By R. H. Whitehead, M. D.,	221
Inorganic Ferments. By Harry C. Jones, Ph. D.,	224
The Sterilization of Catgut. By G. Brown Miller, M. D.,	225
Summaries or Titles of Papers by Members of the Hospital and Medical School Staff appearing Elsewhere than in the Bulletin,	229
Books Received,	229

MORBID CONDITIONS CAUSED BY BACILLUS AËROGENES CAPSULATUS.

THE SHATTUCK LECTURE.[1]

By William H. Welch, M. D.,

Professor of Pathology, Johns Hopkins University.

CONTENTS.

Introduction.—Historical.—Nomenclature.—Characters of Bacillus.—Distribution.—Gas-Bubbles in the Blood and Organs.—Emphysematous Gangrene.—Gaseous Abscesses.—Uterine Infections: Emphysema of the fœtus; puerperal endometritis; physometra; emphysema of the uterine wall; puerperal gas-sepsis.—Infections of the Urinary Tract.—Infections derived from the Gastro-intestinal Canal: Local gastro-intestinal lesions; pneumo-peritonitis with and without perforation; hepatic and biliary infections.—Interstitial Emphysema of the Gastro-intestinal, Genito-urinary, and Biliary Tracts.—Pulmonary and Pleural Infections.—Bacillus Aërogenes Capsulatus in the Blood during Life.—Presence of Bacillus Aërogenes Capsulatus without Gas.—Meningitis and Pyogenic Capacity of Bacillus Aërogenes Capsulatus.—Cavities in the Brain.

Although the subject which I have chosen for this lecture relates for the most part to infrequent affections, the scientific and practical interest attaching to them is considerable and varied. Many instances of the presence of free gas in parts of the body where it does not normally occur and in association with various diseases were recorded by writers of past centuries and were even then the subject of much speculation. The discussion turned generally around the question whether the gas was atmospheric air or the result of putrefaction—a question which in most cases could be solved only by bacteriological examinations. The most numerous and important of such examinations have been made during the last decade, and, although these have left problems still unsolved, they have corrected many current errors and have shed a flood of light upon conditions which were formerly among the most mysterious in pathology.

While it has been demonstrated that various bacteria may be concerned in producing gaseous affections, it is now evident that the bacillus which I discovered in 1891, and to which I gave the name Bacillus aërogenes capsulatus, is the one whose causative agency is best established and most frequently in action. What I shall say will relate mainly to this micro-organism and its pathogenic effects.

Historical.—As a certain amount of confusion concerning

[1] Delivered before the Massachusetts Medical Society, June 12, 1900.

the dates of the first publications[2] on this bacillus exists in foreign literature on this subject, it may be well to state that I reported my observations in November, 1891, to the Johns Hopkins Hospital Medical Society and that the full report of these observations and of the characters of the bacillus was published in July-August, 1892, by Dr. Nuttall and myself.[3] E. Fraenkel's first publication[4] was a short preliminary one which appeared in January, 1893, and was followed in the same year by his valuable monograph on gaseous phlegmons.[5] In August, 1893, one year after the publication of the paper by Nuttall and myself, appeared simultaneously the interesting articles of P. Ernst[6] and of Graham, Steward and Baldwin[7] on foamy organs. Early in 1894 Mann published from my laboratory an observation of emphysematous gangrene caused by Bacillus aërogenes capsulatus,[8] and in January, 1896, Dr. Flexner and I published an extensive paper reporting twenty-three human cases, including not only six personal observations of emphysematous gangrene but also examples of submucous gas-cysts, pneumoserositis, and various other pathogenic manifestations of this bacillus.[9] In July, 1895, appeared Goebel's preliminary communication,[10] and in the following year his full paper on the bacillus of foamy organs.[11] Of the subsequent records the most numerous and valuable have appeared in this country, although they appear to be little known to most European writers.[12] I shall have occasion to refer later to many of these publications, among which those of Dunham, Dobbin, Norris, Bloodgood, Howard, Nicholls, and Pratt and Fulton, may here be mentioned as especially valuable.

Nomenclature.—Dr. Fraenkel has kindly favored me with cultures of the bacillus which he isolated from gaseous phlegmons and to which he gave the name "Bacillus phlegmones emphysematosæ." There can be no question whatever but that his bacillus is identical with our Bacillus aërogenes capsulatus, a point upon which we are both agreed, and which is also made certain by Goebel's studies under Fraenkel's supervision. According to the generally accepted principles of the nomenclature of zoological and botanical species, the name "Bacillus aërogenes capsulatus," as being the first one applied, should be preferred to that of Bacillus phlegmones emphysematosæ. It is, moreover, as pointed out by Muscatello, not open to the objection of implying exclusive relationship to a single disease, as is the case with Fraenkel's designation of the bacillus. As a matter of fact, as we shall see, the capacity to produce gaseous phlegmons is only one of many pathogenic manifestations of Bacillus aërogenes capsulatus. Unfortunately I think that we both erred against the canons of botanical nomenclature in using a trinomial rather than a binomial name for a species.[13]

Characters of Bacillus.—Since our first publication only one material addition has been made to the extended description given by Welch and Nuttall of the morphological and cultural characters of Bacillus aërogenes capsulatus or the gas-bacillus as I shall briefly call it.[14] Fraenkel noted the presence of spores in a few of the bacilli growing in one lot of agar containing sodium formate, and in 1897 Dunham[15] observed spores, with all of the specimens studied, in blood-serum cultures, but not in other media.

Our further studies of the gas-bacillus obtained from different sources have shown a moderate range of variation in some of its properties. This is true especially of spore-formation, rapidity of liquefaction of gelatine, presence of capsules and virulence.

[2] Levy's description in 1891 (Deutsche Ztschr. f. Chirurg., XXXII) of "kleine, feine" bacilli, cultivated from a gaseous abscess and growing in long threads and chains only at body temperature and cultivable only in the first generation, without animal experiments, cannot be accepted as an identification of B. aërog. capsulatus, or indeed be readily reconciled with its characters.

[3] Bulletin of the Johns Hopkins Hospital, 1892, III, p. 81.

[4] Centralbl. f. Bakter., XIII, p. 13.

[5] Ueber Gasphlegmonen. Hamburg u. Leipzig, 1893.

[6] Virchow's Archiv, CXXXIII, p. 308.

[7] Columbus Med. Journ., XII, p. 55.

[8] Annals of Surgery, XIX, p. 187.

[9] Journal of Experimental Medicine, 1896, I, p. 5.

[10] Centralbl. f. allg. Path. u. path. Anat., VI, p. 465.

[11] Jahrb. d. Hamburgischen Staatskrankenanstalten, IV.

[12] Thus v. Hibler in 1899 (Centralbl. f. Bakt., XXV, p. 513 et seq.), in an elaborate study of pathogenic anaërobes, is entirely ignorant of our work and that of other American investigators on B. aërog. capsulatus. The information of Hitschmann and Lindenthal (Sitzungsb. d. k. Akad. d. Wiss., Math.-Naturw. Cl., Wien, 1899, CVIII, Heft 3, Abth. III, p. 67) on the American work is secondhand and both incomplete and inaccurate, in these respects being in unfavorable contrast to that of Muscatello, assisted by Gangitano (Riforma Med., 1900, II, p. 508 et seq.), who write also on the subject of emphysematous gangrene. Knowledge of Bacillus aërogenes capsulatus, under the name "Bacillus perfringens" (Veillon and Zuber), has begun to appear in France in the last two years, but without evidence of acquaintance with the American publications. Even allowing for the great difficulties in keeping pace with the literature of any subject in medicine, a decade would certainly seem sufficient for the light to penetrate even into dark places.

[13] Migula, who, with considerable success, has attempted to reform bacteriological nomenclature, has given the binomial names "Bacterium Welchii" to Bacillus aërogenes capsulatus and "Bacterium emphysematosum" to Bacillus phlegmones emphysematosæ (System der Bakterien, II, pp. 392 and 383, Jena, 1900). He is, however, in error in describing this organism under two different names, as his Bacterium Welchii and Bacterium emphysematosum are identical.

[14] As regards these characters it will suffice here to say that the microorganism is a rather coarse, non-motile, anaërobic bacillus; stains by Gram; grows on all of the ordinary culture-media under anaërobic conditions, best at body temperature, but also at room temperature; liquefies gelatine slowly; forms spores constantly according to the race and the culture-medium, and is capable of generating gas not only by fermentation of sugars but also from proteids. The full description of the characters may be found in Welch and Nuttall's paper.

[15] Bulletin of the Johns Hopkins Hospital, 1897, VIII, p. 68.

While some specimens of the bacillus seem never to form spores on any culture-medium, others, and these appear to be the more common, do so occasionally, especially upon blood-serum, in mannite bouillon, and on plain agar. In animals inoculated with pure cultures we have not observed spore-bearing bacilli.

As a rule the bacillus liquefies gelatine slowly but some specimens do so scarcely at all, and others with fair rapidity. In our first communication we noted peptonization and softening of the gelatine, but this was so slow and slight with the particular specimen studied that we then preferred to class the bacillus among the non-liquefiers. Further experience has shown that the bacillus is a liquefier, but generally a slow one.

As stated in our original article, capsules are not constantly present, but I have generally found no difficulty in demonstrating them in the situations and by the method described by us, and, with the exception of Hitschmann and Lindenthal, most other investigators have been able to demonstrate capsules, when these are searched for by suitable methods.

While the bacillus is to be ranked among those which stain by Gram, it is sometimes rather noticeable in coverslips from cultures that among well stained bacilli, others are partly or wholly decolorized, and this may be observed in members of a single chain. In the tissues the bacilli stain well by Gram. Differences in the viability of cultures were pointed out in our first paper.

It sometimes happens that original cultures from human beings show only a feeble growth, with relatively weak power of gas-production, while subsequent cultures, especially those obtained after passage through the animal body, present the usual vigorous growth and other typical characters. Pratt and Fulton,[16] from a typical case of foamy organs with gas throughout the body, were unable to cultivate the bacillus at all, although twelve anaërobic culture tubes containing various media were inoculated from different parts of the body. This negative result they attribute to the fact that the body had lain in a cold storage vault for sixteen hours after death, an explanation which has some support in an observation previously reported by Welch and Flexner, but still seems hardly satisfactory, as under like conditions the bacillus has been often cultivated.

Lactose, glucose and saccharose are all fermented by the gas-bacillus, the first with the largest production of gas and the last with the smallest. The gas, according to Dunham's analyses, is composed approximately of 64 per cent hydrogen, 28 per cent carbon dioxide, and 8 per cent of a residual gas believed to be mainly nitrogen. It has no foul odor. The amount of hydrogen always greatly predominates over that of carbon dioxide. There is apparently no fermentation of mannite, at least the gas is not appreciably more than in sugar-free media.

E. Fraenkel in 1893 was the first to demonstrate the etiological relation of the gas-bacillus to gaseous phlegmons, our previous investigations being concerned mainly with the so-called foamy organs (Schaumorgane) and the presence of gas in the blood, our results being confirmed a year later by P. Ernst. Soon after Fraenkel's publication we were able to confirm his discovery of the causation of gaseous phlegmons by Bacillus aërogenes capsulatus, and to repeat with like results his animal experiments.

Material or cultures fresh from the infected body are usually highly virulent for guinea-pigs, pigeons and sparrows (E. Fraenkel), which succumb to arpidly spreading local necrosis of the tissues with abundant development of gas, the bacilli invading the blood during life only in small numbers or not at all. There is more or less bloody œdema, but otherwise little inflammatory reaction, leukocytes being present usually only in small numbers in the exudate. Rabbits and mice, while not wholly immune, are far less susceptible than guinea-pigs and pigeons. Dr. Lanier in my laboratory in 1896 succeeded in producing typical gaseous phlegmons around the fractured bones of rabbits inoculated intravenously with pure cultures, and Muscatello has obtained the same results. There are considerable differences in the degree of virulence of the bacillus even in fresh cultures, and old ones may be of very slight virulence.

One of the most interesting and valuable tests of the gas-bacillus is its power of producing gas abundantly in the blood, organs and tissues of rabbits killed a few minutes after intravenous injection, a power not possessed by colon bacilli. The differential value of this test is as great as that of cultures in fermentation tubes. The blood and tissues of the dead rabbit make the culture-medium, the body of the animal takes the place of the test tube, the inoculation is an aseptic one, the bacteria are spread by the blood-current and the conditions are anaërobic. This procedure, which was introduced by Nuttall and myself and has been fully described by us, we have found useful under proper precautions in isolating the gas-bacillus, in separating it from other bacteria which may resemble it, and in the demonstration of one of its most fundamental characteristics, namely, the power to produce gas from proteid material.

Among the points distinguishing the bacillus of malignant œdema from Bacillus aërogenes capsulatus may be mentioned the following: The malignant œdema bacillus is somewhat thinner; has greater tendency to grow into filaments; is less readily stained by Gram; produces spores regularly in culture-media; is motile; liquefies gelatine much more rapidly; produces a foul odor; generates less gas in lactose bouillon; clots and then peptonizes casein; generates little or no gas in rabbits inoculated intravenously and then killed; and by subcutaneous inoculation in susceptible animals causes spreading bloody œdema with little or no development of gas-bubbles, and appears after death in filaments on serous surfaces.

The bacillus to which Lindenthal[17] has quite unnecessarily given the name Bacillus emphysematis vaginæ is doubtless identical with Bacillus aërogenes capsulatus. The same is

[16] Boston Med. and Surg. Journ., June 7, 1900, p. 599.

[17] Wiener klin. Wochensch., 1897, p. 3, et seq.

true of Veillon and Zuber's[18] Bacillus perfringens found by them in appendicitis, by Guillemot[19] in gaseous gangrene and by Soupault and Guillemot[20] in gaseous abscesses, and of Buday's[21] Bacillus cadaveris butyricus, and Cesaris-Demel's[21a] bacillus, both found in foamy organs. I am strongly inclined to the opinion that the anaërobic bacillus isolated by Achalme and others from the blood and tissues of several cases of acute articular rheumatism and found by Savtchenko and Mielkich in the soil is likewise identical with our gas-bacillus.[22] As will be considered later, Gwyn has cultivated Bacillus aërogenes capsulatus also from the blood of a choreic patient during life.

Distribution.—The surmise expressed by Welch and Nuttall that the gas-bacillus is widely distributed in nature has since been confirmed. The natural habitat of the organism is the intestinal canal and the soil, the homes of so many other anaërobic bacteria. Welch and Flexner in 1896 brought evidence of the presence of the bacillus in both of the situations mentioned. Clopton of the Johns Hopkins Hospital has found the bacillus twice in the normal appendix vermiformis. Howard[23] has recently reported the presence of morphologically identical bacilli in the intestines of twenty-five consecutive human cases examined post mortem, and in ten of these he demonstrated the bacillus by cultures and inoculation of animals. The same conclusion concerning the regular presence of the bacillus in the intestine has been reached by Hitschmann and Lindenthal. The gas-bacillus has been repeatedly cultivated from the intestine in my laboratory, but we have made no systematic study of the frequency of its presence.[23a] I have found the bacillus also in the intestines of rabbits, dogs and swine, and here it is interesting to note the frequency with which submucous gaseous blebs are found in the pig's intestine at autopsy.

In 1896 Dr. Walker, at the Johns Hopkins Hospital, succeeded in finding Bacillus aërogenes capsulatus in dust collected by sweeping floors, proving its presence both by cultures and animal experiments. My assistant, Dr. Harris, has cultivated the bacillus from the contents of an old cesspool. I had previously reported in 1896 the isolation of the bacillus from a bullet removed from the head of the tibia in a case of gaseous phlegmon, and E. Fraenkel[24] has cultivated the gas-bacillus from a splinter of wood extracted from a wound in a case of tetanus. These observations confirm the natural inference to be drawn from the study of cases of traumatic emphysematous gangrene, in most of which the source of infection is manifestly foreign material, especially dirt, in wounds. In the light of these demonstrations of the wide distribution of the gas-bacillus in the outer world and in fæces, the conclusion is warranted that it must occasionally be present upon the human skin.

We are not informed whether there are differences in the regional distribution of the gas-bacillus. The fact that during the last decade a larger number of cases of emphysematous gangrene have been reported from Baltimore than from any other single locality is due probably to our interest in the subject and consequent search for cases. The bacillus has been found not only in America and Europe, but Dr. Flexner has brought reports of three infections with the gas-bacillus in Manila observed during a stay of three months.

Gas-bubbles in the Blood and Organs.

We turn now to the consideration of the various conditions in which Bacillus aërogenes capsulatus has been found in human beings. We need not pause to consider the occasional presence of this bacillus in ordinary cadaveric decomposition, a circumstance sufficiently explicable by the occurrence of this organism in the healthy intestinal canal.

Of an entirely different nature are the cases in which gas-bubbles are found in the blood and organs within a few hours after death and without any trace of ordinary putrefaction. Such a condition has been recognized at autopsies as soon as one, two, three, five, eight hours after death. It may occur not only after death from gaseous phlegmon, when, however, it is by no means constant, but also after death from the most varied causes. It has been observed repeatedly in autopsies on pregnant and puerperal women, especially after death from abortion and acute sepsis. Cases reported by Cless,[25] Jürgensen,[26] Vachetta,[27] Dunin,[28] Vogel[29] and others as examples of entrance of air or gas into the circulation from gastric ulcers, typhoid or dysenteric ulcers, pulmonary tuberculosis, in septicæmia and various other diseases, find now their natural explanation in the invasion of gas-bacilli, instead of in the curious hypotheses propounded by the authors cited. In all probability, although I have had no opportunity to observe such a case, the free gas which has been repeatedly found in

[18] Arch. de méd. exp., 1898, X, p. 539.

[19] Compt. rend. Soc. de biol., 1898, 10. s., V, p. 1017.

[20] Bull. et mém. Soc. med. d. hôp. de Paris, 1900, 3. S., XVII, p. 216.

[21] Centralbl. f. Bakt., 1898, XXIV, p. 369.

[21a] Giornale d. R. Accad. di med. di Torino, 1898, LXI, p. 256 and LXII, p. 190.

[22] Achalme, Ann. de l'Inst. Pasteur, 1897, XI, p. 845; Pic and Lesieur, Journ. de phys. et de path. gén., 1899, I, p. 1007, and Savtchenko and Mielkich, Arch. russes de path., 1899, VIII, p. 145.

[23] Contributions to the Science of Medicine dedicated by his pupils to William Henry Welch on the 25th Anniversary of his Doctorate, p. 461, Baltimore, 1900.

[23a] Mr. Hirshberg is now engaged in my laboratory in a study of the distribution of the gas-bacillus in human and animal intestines and in the outer world and will report his observations later.

[24] Münch. med. Woch., 1899, Nos. 42 and 43.

[25] Luft im Blute, Stuttgart, 1854.

[26] Deutsches Arch. f. klin. Med., 1882, XXXI, p. 441, and 1887, XLI, p. 569.

[27] Sull' embolismo gazoso per penetrazione d'aria nel sistema circolatorio, Pisa, 1880.

[28] Berliner klin. Woch., 1882, p. 11.

[29] Ibid., 1882, p. 187.

the blood-vessels and heart after deaths from chloroform is due likewise to the invasion of the gas-bacillus, and is not, as supposed by Hankel,[20] nitrogen derived from air pressed through the lungs into the pulmonary blood-vessels in violent expiratory movements with closed glottis.

There is every gradation from cases with a few bubbles of gas in the blood or tissues to those with extensive emphysema of the organs and tissues. The term "foamy organs" (Schaumorgane of the Germans) may be applied to the latter condition. The liver is the organ most frequently the seat of early and abundant development of gas, but there is no definite rule as to the distribution and amount of gas in different cases. The gas may be limited to the abdominal veins or to the pulmonary vessels or to one of the cardiac cavities, or be found only in the tissues at one place, especially near the stomach or intestine. It is more abundant in the veins than the arteries, and may be only in the former. As will be explained later the invasion in the majority of cases is from the intestine. That the gas-bubbles may be dislocated from their original position in liquid and soft material in the body is self-evident, but I have not found them unassociated with gas-bacilli

Formerly this early presence of free gas in the heart and vessels, without evident post-mortem decomposition, was very generally explained by the assumption of entrance of air into the circulation, even when no portal of entry could be found.[21] The most extensive application of this explanation was made in the pregnant and puerperal cases. It is remarkable that the first case of this nature to be examined bacteriologically was that reported by me in 1891. In this and in nearly all subsequent similar cases with satisfactory bacteriological examination Bacillus aërogenes capsulatus was found.

The main questions which arise concerning the interpretation of these cases are whether the invasion of the bacilli and whether the development of the gas are ante-mortem or post-mortem phenomena.

Rabbits survive the introduction of large numbers of gas-bacilli directly into the circulation, unless there exists somewhere in the body necrotic or damaged tissue offering little or no vital resistance. If the animal be killed within a few minutes after the intravenous injection of the bacilli and kept in a warm place, there are abundant multiplication of the bacilli and large development of gas throughout the body within the space of six or eight hours; whereas if the bacilli be introduced at one point, as for example the right heart, of a rabbit just killed, it takes a much longer time, often twenty-four to forty-eight hours, for gas and bacilli to make their appearance at points far distant from the seat of inoculation. It seems justifiable to draw from these three groups of experiments, which have been fully reported by Welch and Nuttall, the conclusion that when bacilli and gas are found within a few hours after death widely distributed in the body, the gas-bacilli have entered the circulation during life, but probably in most cases only shortly before death.

There is one factor, however, to be considered which is absent in the experimental cases and may be present in human beings, to wit, the quick disappearance of the bactericidal power of the blood. This factor is an important determinant of the rapidity of onset of post-mortem decomposition. Very soon after death from certain diseases, and particularly from snake-venom, bacteria may make their appearance in the blood and organs. An explanation of these cases is furnished by the experiments of Ewing and myself,[22] which demonstrated that the blood of rabbits killed by rattlesnake venom is practically devoid of bactericidal power, so that immediately after or even shortly before death bacteria can start growing in the body as they would in a tube of beef-broth. But after all due allowance has been made for the possible reduction or loss of bactericidal power of the blood, I still consider that it is not possible to explain some of the cases in which bacilli and gas have been found in the heart, blood-vessels and organs very soon after death, especially when the corpse has been kept in a cold place, otherwise than upon the assumption of the distribution of the bacilli by the circulating blood.

It is another question whether gas as well as bacilli may be present in the circulating blood and internal organs during life in the class of cases now under consideration, and I regret to be unable to furnish a positive answer to this question. I do not see how an affirmative answer can be obtained otherwise than by the actual demonstration of gas in these situations either during life or immediately after death. Gas-bubbles and bacilli have been found in the heart and vessels within an hour after death, but that is time enough for bacilli which have already been introduced to multiply and begin to form gas. I at first thought that absence of nuclear staining around the gas-bubbles and masses of bacilli might serve as an indication of their presence during life, and this view is advocated by P. Ernst, but I have since learned from experiments on rabbits that this is not a decisive criterion, although often both in rabbits and in human beings there is no defect in nuclear staining around bacilli and gas-bubbles.

I know of no other pathogenic microorganism which offers such difficulties in determining whether its effects in the interior of the body have been produced before or after death. The difficulty arises from the circumstances that these effects in most cases and most situations consist almost entirely in local necrosis and formation of gas, whether the invasion and growth of the bacilli be before or after death, and that unlike most pathogenic bacteria the gas-bacillus grows better in the dead than the living body. Possibly some importance in the solution of the problem may attach to the demonstration of emboli of liver cells and of bone-marrow cells which were in enormous numbers in the pulmonary vessels in a case of gaseous phlegmon of the sub-mammary tissues following infusion of salt-solution. At the autopsy made by Dr. Carroll

[20] Cless. Luft im Blute. Stuttgart, 1854, and Couty. Thèse, Paris, 1875.

[21] Lancet, 1894, I, p. 1236.

the liver and other organs were emphysematous. Further observations with reference to these emboli in this class of cases are needed.

I do not consider that there is any inherent improbability in the supposition that gas-bubbles may be in the circulating blood during life without causing speedy death from gaseous embolism. It is only when a large volume of air is introduced quickly into the blood-current that sudden death results from air-embolism. Very exaggerated ideas have prevailed among physicians as to the dangers from the entrance into the circulation of small quantities of air. Laborde and Muron[33] injected into the external jugular vein of a dog 1120 cc. of air in the space of one hour and a half without causing death, and Jürgensen,[34] into the left femoral artery of a narcotized dog weighing 43½ kilo, 3650 cc. in the space of two hours and twenty-five minutes with only slight disturbance of the respiration and of the action of the heart. Hare,[35] on the basis of experiments, likewise controverts current beliefs concerning the dangers from entrance of a moderate quantity of air into the veins.

I have come across in the older literature from the days when venesection was a common practice, reports of cases in which blood containing bubbles of gas escaped during venesection from veins of the arm.[36] In none of these was there evidence that air had gained entrance to the circulation. Maisonneuve,[37] in incising two gaseous phlegmons of the thigh following compound fracture, observed the escape of blood containing gas-bubbles from the cut veins and was able to trace the gas within the veins for a long distance.

It seems to me very improbable that an anaërobic bacillus, such as the gas-bacillus, can multiply in the circulating blood, still this bacillus is less sensitive to the presence of oxygen than many anaërobes, and we do not know whether the loose combination in which oxygen is present in the blood would necessarily prevent its growth under all circumstances.

I see no reason why this bacillus might not multiply and form gas in the liver, spleen and most other internal organs, as we know it can do in parts open to inspection during life. We have positive evidence in the cases reported by Graham, Steward and Baldwin and by Dunham that gas-bacilli may be conveyed by the circulation from an infected portal of entry—in the one case the puerperal uterus and in the other a urethral wound—to distant parts of the body and there produce subcutaneous emphysema and necrosis. There is no part of the body which offers such favorable conditions for the post-mortem growth of the bacillus as the liver, probably on account of its content of carbohydrate, and, if the liver like the integuments were open to inspection during life, I believe that we should find evidence that in certain cases the emphysema of this organ, which is such a conspicuous post-mortem phenomenon in instances of invasion by the gas-bacillus, had begun during the life of the patient. As will be considered subsequently emphysema of mucous membranes open to inspection, we know can exist during life.

In the great majority of the instances, however, in which gas-bubbles are found in the blood and internal organs at autopsy the evidence is in support of the view that the development of the gas is a purely post-mortem phenomenon. Certainly the greatest caution should be exercised in the interpretation of any such cases as vital processes, even in early autopsies without ordinary putrefaction. One thing which our investigations have established is that the finding of gas-bubbles in the blood-vessels and heart within so short a time as one hour after death furnishes in itself no proof of the entrance of air into the circulation. Especially is it to be emphasized that the limitation of gas to the right heart and adjacent vessels may occur in cases of invasion by the gas-bacillus and is not, as is often represented, peculiar to air-embolism. I shall refer later to the question of gaseous embolism in cases of emphysematous gangrene and of physometra.

Emphysematous Gangrene.

In a few instances we have found in wounds, usually compound fractures or gunshot injuries, in which dirt had gotten in, Bacillus aërogenes capsulatus without the presence of gas or other evidence that the bacillus was producing any characteristic effects.[38] Such cases have always been watched by the surgeons with anxiety, and it is probable that at least in some the early recognition of the bacillus followed by free incisions and thorough cleansing and disinfection has warded off a subsequent grave infection. In view of the wide distribution of the gas-bacillus in the outer world and in the intestinal contents it is probable that it must not so very infrequently gain access to wounds without securing a foothold. While this innocent behavior, with which we are also familiar in the case of the tetanus bacillus, may sometimes be due to attenuated virulence of the bacillus, it is probably oftener attributable to accessory circumstances, such as the resistance of the patient, the condition of the wound and surrounding tissues, and lack of association with suitable microorganisms and foreign substances.

It is as a cause of that most dreaded of wound complications, emphysematous gangrene, that Bacillus aërogenes capsulatus especially claims the interest of surgeons. The classical clinical descriptions of this disease we owe to Maisonneuve[39] and to Pirogoff,[40] the former giving to it the name

[33] Comptes rend. Soc. de la biol., 1873, V.

[34] Deutsches Arch. f. kl. Med., 1882, XXXI, p. 458.

[35] Therap. Gazette, 1889, 3. S., V, p. 606.

[36] Marshall's case reported by May, Trans. Path. Soc., London, 1858, IX, p. 157; Durand-Fardel's case also cited by May, and Pirogoff's case in his Grundzüge d. allgem. Kriegschirurgie, p. 1063, Leipzig, 1864.

[37] Cited from Hitschmann and Lindenthal, Sitzungsb. d. k. Akad. d. Wiss., Math.-Naturw. Cl., Wien, 1899, CVIII, iii, 3, p. 67.

[38] Such cases have been reported by Bloodgood from the Johns Hopkins Hospital in Progressive Medicine, 1899, IV, December, p. 158.

[39] Gaz. méd. de Paris, 1853, p. 592.

[40] Grundzüge d. allgem. Kriegschirurgie, pp. 867 and 1006, Leipzig, 1864.

"gangrène foudroyante," and the latter designating it "primary mephitic gangrene" or "acute gangrenous œdema." Among other more or less common designations are "emphysematous or gaseous gangrene," "gaseous phlegmon," "septic emphysema," "érysipèle bronzé" (Velpeau), "progressive gangrenous œdema," "gangrenous septicæmia," and "emphysematous cellulitis."

This wound complication was more common in preantiseptic times, especially in military surgery, than it is to-day, but at least 70 cases have been reported during the last quarter of a century. In prebacterial days the affection was attributed by some writers to the penetration of air into the tissues, but by most to the decomposition of the tissues, particularly of adipose tissue and bone-marrow, brought by an injury into contact with the atmosphere.

Bottini[1] in 1871 was the first to demonstrate the infective nature and transmissibility of emphysematous gangrene.

Later Gussenbauer[2] also recognized the disease as a definite infection and attributed it to the bacteria of putrefaction. After Pasteur's discovery in 1877 of his "vibrion septique," more commonly, since Koch and Gaffky's investigations, designated Bacillus œdematis maligni, and especially after Chauveau and Arloing's[3] paper in 1884, cases of emphysematous gangrene have been usually reported, especially in France, as instances of Pasteur's gangrenous septicæmia or Koch's malignant œdema. W. Koch's[4] attempt to identify the disease with symptomatic anthrax (Rauschbrand) was based on faulty bacteriological studies and has met with no confirmation. In 1884 F. J. Rosenbach[5] reported finding in coverslip specimens from two cases of traumatic emphysematous gangrene coarse bacilli, some of which had terminal spores. These he was unable to cultivate, only aërobic methods being employed. It is probable that Rosenbach saw Bacillus aërogenes capsulatus in these cases, but without distinguishing it from associated spore-bearing bacilli.

A critical examination of the records of alleged malignant œdema in human beings shows that in very few was the organism concerned satisfactorily identified as the genuine malignant œdema bacillus. Very often it has been simply assumed without more than a microscopical examination that bacilli found in spreading œdematous conditions with or without gas have been those of malignant œdema, and even where cultures and animal experiments have been employed the descriptions are frequently so meagre as to leave the identity of the organism wholly in doubt. In France it is usually assumed without any discussion and even without any bacteriological examination that gangrène foudroyante is malignant œdema (Pasteur's septicæmia),[6] and the same ignorance of the present status of this subject is still sometimes encountered in England, Germany and elsewhere. Nevertheless the investigations of the last seven years, beginning with those of E. Fraenkel and soon followed by observations of myself and collaborators, have demonstrated that by far the most common and important specific cause of gaseous phlegmons or emphysematous gangrene is Bacillus aërogenes capsulatus.

Whether the bacillus of malignant œdema can produce an identical or similar anatomical and clinical affection in human beings I regard as an unsettled question. It is certainly remarkable in view of current doctrines in text-books that neither E. Fraenkel nor I, with our relatively large experience, nor indeed, so far as I am aware, any one who has made himself thoroughly acquainted with Bacillus aërogenes capsulatus, has encountered an instance of emphysematous gangrene in man caused by the bacillus malignant œdema. The whole subject of human malignant œdema is one which needs thorough revision and investigation by more exact bacteriological methods than have yet been applied to it.[7] I have already mentioned the chief points of difference between the bacillus of malignant œdema and Bacillus aërogenes capsulatus.

There is a relatively small group of cases of gaseous phlegmon attributed by those reporting them[8] either to the colon bacillus or the proteus bacillus. In most of these cases anaërobic culture methods were not employed. No one has succeeded in producing experimentally gaseous phlegmon with either of these bacilli, and I think there is good reason to be skeptical concerning their capacity to produce this disease, unless perhaps Bacillus coli may do so in diabetics.

It is possible that some of those reporting the colon bacillus as the cause of emphysematous gangrene may have confounded with it a facultative anaërobic bacillus which we have isolated from two cases of this disease, and which has been studied in my laboratory by Dr. Lanier. It resembles in anaërobic cultures very closely Bacillus aërogenes capsulatus, but it is capable of aërobic growth also, and then the rods are thinner and more like colon bacilli. It has the power of producing gas abundantly in the blood and tissues of rabbits killed a few minutes after intravenous injection, a power not possessed by genuine colon bacilli. I have already spoken of

[1] Gior. d. r. Accad. di med. di Torino, 1871, 3. S., X, pp. 1121 and 1138.

[2] Deutsche Chirurgie, Lief. 4, Stuttgart, 1882.

[3] Bull. Acad. de Méd., 1884, 2. S., XIII, p. 604.

[4] Deutsche Chirurgie, Lief. 9, Stuttgart, 1886.

[5] Die Mikroorganismen bei den Wund-Infections-Krankheiten des Menschen, Wiesbaden, 1884.

[6] An exception is Guillemot (Compt. rend. Soc. de biol., 1898, 10. S., V, p. 1017) who has found B. aërog. caps. (B. perfringens) in a case of gaseous gangrene and who controverts the prevalent view of French authors who attribute this disease exclusively to Pasteur's vibrio.

[7] In the case reported recently by Brabec (Wiener klin. Rundschau, 1900, XIV, pp. 145 and 167) the identification of the malignant œdema bacillus seems satisfactory. Here there was extensive bloody œdema without gas, so that the case was not one of emphysematous gangrene. On the other hand, Hämig and Silberschmidt (Correspondenzbl. f. Schweizer Aerzte, 1900, XXX, p. 361) bring no proof of any consequence that they were dealing, as they supposed, with the malignant œdema bacillus in two cases of gangrène foudroyante.

[8] Chiari, v. Dungern, Bunge, Klemm, Hlava, Evans, Grasberger, Hauser, Margarucci, Muscatello, Hitschmann and Lindenthal.

the importance of this test, which has been employed by none of the writers who have claimed to find colon bacilli as the cause of gaseous phlegmons. This bacillus, when virulent, is capable of causing the same spreading and fatal emphysematous necrosis in guinea-pigs and pigeons as is Bacillus aërogenes capsulatus.

I have been accustomed to speak of this bacillus, to which I have called attention in previous publications, as the aërobic variety of our gas-bacillus. I believe, however, that it is identical with Sanfelice's Bacillus pseudo-œdematis maligni,[49] with which he is inclined to identify Klein's "new bacillus of malignant œdema."[50] Chavigny[51] has isolated apparently the same bacillus, which he likewise identifies with Sanfelice's Bacillus pseudo-œdematis maligni (not to be confounded with the pseudo-œdema bacillus of Liborius), from a case of gaseous gangrene, and he also calls attention to the probability that others may have mistaken it for the colon bacillus. While, therefore, unwilling upon existing evidence to accept the colon bacillus as a demonstrated cause of gaseous gangrene (except perhaps in diabetics), I am of the opinion that an aërobic bacillus, probably identical with Sanfelice's Bacillus pseudo-œdematis maligni, is capable of producing this affection, but it is much less frequently concerned than Bacillus aërogenes capsulatus.

I have collected 46 caes of emphysematous gangrene, in all of which Bacillus aërogenes capsulatus was demonstrated, and, therefore, all reported or observed during the last seven years.[52] This is a far larger number of cases than has ever been brought together before.

Thirty-two are reported by American observers and only 14 by foreign investigators. Of the former group of cases 16 were observed in Baltimore, most of the cultures having been studied in my laboratory; of the foreign group of cases all are reported from Germany, Austria, Italy and France, 4 by E. Fraenkel, 1 (not absolutely certain) by Passow, 5 by Hitschmann and Lindenthal, 3 by Muscatello assisted by Gangitano and 1 by Guillemot.[53]

Cases of gaseous phlegmon in which Bacillus aërogenes capsulatus was not demonstrated are not included, although many of these presented the same clinical characters and doubtless in some at least the gas-bacillus was the active agent. This is true especially of the cases of gangrène foudroyante, usually without satisfactory bacteriological examination, attributed by French writers to Pasteur's vibrion septique. Gertler's[54] eight cases of gaseous phlegmon cannot be utilized for our purposes at all, as they are without any satisfactory bacteriological reports.

A complete analysis of these 46 cases would afford material more than sufficient to occupy this entire address, so that I shall be able to present here only some of the more important points.

Thirty-five of the patients were males, 10 females and of one the sex is not stated. The preponderance of males is to be explained by the fact that most of the cases were due to severe injuries. Robust workmen in the prime of life furnished the largest contingent of cases.

In 80 per cent of the cases one of the extremities was the seat of the emphysematous gangrene, the lower being affected a little over twice as often as the upper extremities. In several instances the emphysema extended from the thigh to the abdominal wall or from the arm to the subcutaneous tissues of the shoulder and chest. There were three examples of primary emphysematous phlegmon of the abdominal wall: of these one following removal of the appendix (Bloodgood), one from an unrecognized strangulated Littré hernia (Martin),and one affecting the deep tissues of a nephrectomy wound (Muscatello). In all of these the infection is believed to have started from the intestine. In one of Dunham's cases there was emphysematous gangrene (originating in a prostatic abscess opening in the buttock) of the scrotum, penis, and anterior abdominal and thoracic subcutaneous tissues. In three instances (Carroll (2); Dobbin (1) reported by Bloodgood) the breast and submammary tissues were the primary

[49] Ann. d. Istit. d'Igiene sper. d. Univ. di Roma, 1891, N. S., I, p. 365, and Ztschr. f. Hyg., 1893, XIV, p. 352.

[50] Centralbl. f. Bakter., 1891, X, p. 186.

[51] Ann. de l'Inst. Pasteur, 1897, XI, p. 860. Perhaps the bacillus found by Foà and Bonome (Ztschr. f. Hyg., 1889, V, p. 403) in a case of anthrax-like septicæmia with gas in the tissues was Sanfelice's bacillus. Roncali in the Italian translation of Senn's Surgical Bacteriology (Bacteriologia Chirurgica, p. 109) also claims Sanfelice's bacillus as a cause of gaseous gangrene.

[52] This list includes 16 cases observed in Baltimore, mostly at the Johns Hopkins Hospital, of which 2 are unpublished, and the remaining 14 have been published by Mann (1), Ann. Surg., 1894, XIX, p. 187; Welch and Flexner (6), Journ. Exp. Med., 1896, I, p. 5; Martin (1), University Bulletin, 1896, I, No. 3, and Bloodgood (6), Progressive Medicine, 1899, IV, December, p. 158. The notes of an additional unpublished case observed in Manila have been given me by Dr. Flexner. There are also 3 unpublished cases for the records of which I am indebted to Dr. Carroll of Washington.

The references to the remaining 26 cases are as follows: E. Fraenkel (4), Ueber Gasphlegmonen, Hamburg u. Leipzig, 1893; Passow (1), Charité-Annalen, 1895, XX, p. 275; Dunham (5), Bulletin of the Johns Hopkins Hospital, 1897, VIII, p. 68; Ferguson (1), Trans. Indiana Med. Soc., 1897, p. 339; Erdmann (1), Med. Record, Feb. 5, 1898, p. 205; Le Boutillier (1), Med. Record, March 5, 1898, p. 353; Love and Cary (1), Med. Record, April 8, 1899; Norris (1), Amer. Journ. Med. Sc., 1899, CXVII, p. 195; Hitschmann and Lindenthal (5), Sitzungsb. d. k. Akad. d. Wiss., Math.-Naturw. Cl., Wien, 1899, CVIII, Hft. iii, Abth. iii, p. 67; Thorndike (2), Boston Med. and Surg. Journ., June 7, 1900, p. 592; Muscatello with Gangitano (3), Riforma med., 1900, II, pp. 508, 519 and 530; Guillemot (1), Compt. rend. Soc. de biol., 1898, 10. S., V, p. 1017. A few other cases in which the gas-bacillus was found are not reported with sufficient detail to be available for analysis. It is safe to say that B. aërog. caps. has now been found in over 50 cases of gaseous gangrene.

[53] Soupault and Guillemot (Bull. et mém. Soc. méd. d. hôp. de Paris, 1900, 3. S., XVII, p. 216) have reported two gaseous abscesses following hypodermic injections, and a third which they regard as metastatic, in which they found the gas-bacillus (B. perifringens), once in pure culture. These cases will be considered subsequently under the heading "Gaseous Abscesses."

[54] Ueber Gasphlegmonen. Inaug.-Diss. Halle, 1898.

seat of the disease, all of these resulting from the infusion of salt solution. In one case (Dunham) the gaseous phlegmon appeared at the angle of the lower jaw after incision of a foul submaxillary abscess. In one instance (Welch and Flexner) it started within the pelvis from traumatic rupture of the rectum and extended through the sciatic notch down the thigh.

Of especial interest are three examples of multiple or metastatic emphysematous gangrene, one of the forearm and opposite shoulder, another of the thigh and both shoulders, and still another of one shoulder and the buttocks. In the older literature are similar cases; thus Nélaton observed emphysema not only in the injured leg but also in the opposite, uninjured extremity. In 1897 Leech [55] reported without adequate bacteriological examination a case of emphysematous gangrene of the right leg following about three weeks after injury of the right thumb, which became inflamed, there being no evident local cause of the affection of the leg. These cases are to be explained by transportation of the bacilli through the lymphatic or blood-current from the primary focus of entrance.

In all but 5 of the 46 cases the emphysematous gangrene followed traumatism or a surgical operation. The injuries were as follows: compound fractures, 18; bullet and gunshot wounds, 7; infusion of salt solution, 3; hypodermic injections, 2; ligation of the femoral artery for aneurysm, 3; external urethrotomy, 2; traumatic rupture of the rectum, removal of the appendix, prostatic abscess following self-catheterization, operation for strangulated, Littré hernia, incision of a foul submaxillary abscess, and nephrectomy, each 1. Of the 5 non-traumatic cases the gaseous gangrene followed erysipelas in one, was consecutive to apparently spontaneous gangrene in 2, whether diabetic or not is not stated, and was without apparent explanation in two (Fraenkel's Case 2 and Passow).

Compound fractures and next bullet and gunshot wounds occupy by far the most prominent place in this list, each of the other various causes being represented only by scattered cases. Those injuries in which there are much laceration and crushing of tissue, comminution of bone and grinding of dirt, bits of clothing or other foreign bodies into the wound are the ones most likely to be followed by emphysematous gangrene. That, however, severe traumatism is not an essential factor is shown by the 5 cases (10.9 per cent of the entire number) following hypodermic injections and infusion of normal salt solution (see cases also under "Gaseous Abscesses.") These latter, however, were all of patients whose vital forces were greatly depressed, namely, by Asiatic cholera, typhoid fever, surgical shock, or post-partum hæmorrhage. There is good reason to believe that the intact tissues of human beings in health possess marked resistance to the gas-bacillus.

In the great majority of cases it was evident that the gas-bacillus was introduced through the wounded skin from without. In three instances (removal of appendix, strangulated hernia, and traumatic rupture of the rectum) the infection undoubtedly came from the intestine. This was also the probable source of infection in one of Muscatello's cases (gaseous phlegmon in the site of an extirpated kidney). With our present knowledge of the frequent, if not regular, presence of Bacillus aërogenes capsulatus in the intestine, there is nothing surprising in this mode of infection. In three of Dunham's cases the infection followed injury of the urethra, and here also the bacilli may have come primarily from the intestine. In one of his cases (gaseous phlegmon at angle of the jaw) it was suggested that the bacilli gained entrance through decayed teeth.

Bloodgood thinks it probable that in one of his cases the gas-bacilli were brought by the circulation to the seat of infection. In this case the femoral artery was ligated for traumatic arterio-venous aneurysm in the popliteal space. There was no primary infection of the wound, but gangrene of the foot and leg ensued and on incision gas-bubbles were found in the blood of the aneurysmal sac and the tissues. With what we know about the entrance of intestinal bacteria into the circulation, there is nothing improbable in Bloodgood's opinion, which is also supported by Lanier's and Muscatello's experiments already mentioned. The clot in an aneurysm and tissues robbed of their nutrient supply would offer little or no resistance to the growth of bacilli which might reach them or their immediate neighborhood through the circulation and the conditions would be anaërobic. It was indeed a case of aneurysm in which I first found the gas-bacillus, and here the clot was swarming with bacilli. It is interesting to note that three of the cases of emphysematous gangrene in my list followed ligation of the femoral or popliteal artery for aneurysm.

Pirogoff [56] distinguished clinically two groups of cases of traumatic emphysematous gangrene. He described under the name "primary mephitic gangrene" cases in which the emphysema appears within two days after the injury, the "local stupor" passing without inflammatory reaction into crepitating gangrene. Here the emphysematous necrosis spreads rapidly, the patient sinks into collapse with an icteroid hue of the skin, small, thready pulse and cold sweats, and death occurs usually within a few days after the onset. This type of the disease corresponds to Maisonneuve's gangrène foudroyante. In the second group, designated by Pirogoff also as "acute gangrenous œdema," there is reaction from the primary "local stupor" of the tissues, the emphysema is preceded and accompanied by local, œdematous or purulent inflammation, is associated with febrile reaction, often appears later after the injury and spreads less rapidly, and presents in general a more varied anatomical and clinical picture than the first class of cases.

Hitschmann and Lindenthal consider that Pirogoff's first group corresponds especially to cases of pure or predominant infection with the gas-bacillus, and his second group to mixed infections. Erdmann is also of the opinion that in the un-

[55] Quart. Med. Journ. (Sheffield), 1896-97, V, p. 237.

[56] Grundzüge d. allg. Kriegschirurgie, p. 1006, Leipzig, 1864.

mixed infections the emphysematous necrosis spreads more rapidly and is more likely to terminate fatally. On the other hand, Muscatello and Gangitano, who also divide the cases into two groups—pure infections and mixed infections—hold that the mixed infections are characterized by the rapidly progressive form of emphysematous gangrene, while the pure infections, at least in their early stage, show little tendency to spread beyond the injured tissues. According to the last named authors the gas-bacillus is incapable of exerting any pathogenic action upon healthy tissues, but attacks only tissues already altered in their vitality by injury, other pathogenic microorganisms, toxins, or other depressing factors.

The study of our cases has not enabled me to adopt in their exclusive form either of the two conflicting opinions just stated. Of the collected 46 cases, 30 were mixed infections, 14 were pure and of 2 there is no clear statement on this point. The most common associated bacteria were the pyogenic streptococci and staphylococci. Among other forms found occasionally were Bacillus coli, proteus, pyocyaneus, tetanus, Sanfelice's Bacillus pseudo-œdematis maligni, and uncultivable, often spore-bearing, bacilli. It seems probable that the bacillus of malignant œdema, being a common inhabitant of the soil, must occasionally, like the tetanus bacillus, be present, but it was not isolated from any of these cases. My experience is that if reliance be not placed exclusively upon cultures, but careful microscopical examinations be also made, instances of unmixed infection with Bacillus aërogenes capsulatus are rare. It is by no means always easy to determine whether associated bacteria are exerting pathogenic action or not. Pyogenic cocci may be present without producing pus or marked inflammatory reaction.

We have found rapidly progressive forms of emphysematous gangrene both with pure infection with the gas-bacillus and with mixed infections, and on the other hand we have observed with both types of infection cases in which the tendency to spread is much less marked. In all of the cases with much purulent inflammation mixed infection was present, but aside from this feature the division of the cases into pure and mixed infections does not, according to our experience, correspond to different, sharply marked, clinical features. Pirogoff's classification is doubtless of clinical value, but there is every gradation between the two groups.

I cannot agree with Muscatello and Gangitano, whose investigations of emphysematous gangrene are of great value, that the gas-bacillus is incapable of attacking healthy tissues. Virulent cultures, even in moderate doses, can produce rapidly spreading gaseous phlegmons when inoculated into the subcutaneous tissues of susceptible animals such as guinea-pigs and pigeons. In human beings the emphysema may extend very rapidly into the healthy tissues, frequently outstripping in its advance the inflammatory œdema. This may occur in pure, as well as in mixed, infections with the gas-bacillus. After amputation through apparently healthy tissues there may be rapidly spreading emphysema from the stump (Welch and Flexner's Case II). The two instances of meningitis observed by Hitschmann and Lindenthal and by Howard speak also for the power of the gas-bacillus to attack healthy tissues. It is true, as urged by Muscatello and Gangitano, that toxins derived from the bacilli may prepare the tissues for the invasion and action of the advancing bacilli, but the same explanation has been put forward for the spread of other pathogenic bacteria in healthy tissues. In asserting that the gas-bacillus may attack healthy tissues, I would not be understood as minimizing the great importance of the various accessory causes of emphysematous gangrene which act by lowering the vitality of the tissues or the general resistance of the patient, or as failing to recognize the marked resistance to infection by the gas-bacillus offered by the healthy tissues, a resistance to which I have previously called attention and which I shall have occasion further to emphasize.

Gas may appear in the tissues as early as eight hours after the injury. In a case of gaseous phlegmon following a bullet wound of the knee joint, reported by Welch and Flexner, Dr. Bloodgood recognized gas in the joint [37] and surrounding tissues just twenty hours after the injury. In a case of Dr. Tiffany's, which we have reported, death from emphysematous gangrene, due to pure infection with the gas-bacillus, occurred forty-eight hours after a fall causing a compound, comminuted fracture of the patella with grinding of the underclothing into the wound. There was no other injury of the body. Any one who has seen one of these rapidly fatal cases of spreading, traumatic, emphysematous gangrene will receive an impression which he will never forget.

The anatomical and clinical study of uncomplicated emphysematous gangrene demonstrates that the disease is not, as many formerly supposed, simply an intense variety of ordinary phlegmonous inflammation or cellulitis, but is a disease sui generis. It may be combined with phlegmonous inflammation, but then some other microorganism, usually the streptococcus, is associated with the gas-bacillus.

In typical uncomplicated cases the lesions consist in necrosis of all the tissues, the presence of gas in the interstices, infiltration with blood, evidences of the mechanical action of the gas, and exudation of a variable amount of bloody serum. The amount of gas varies much in different cases. There may be only a few bubbles or the tissues may be everywhere blown up with gas. The nuclei disappear by karyolysis. The notable thing in most cases is a nearly complete absence of leukocytes and of cellular reaction, although in a few instances, even of pure infection, I have found leukocytes in considerable number, and even purulent foci, but generally at a distance from the primary necrosis. As will be shown later Bacillus aërogenes capsulatus in certain situations is capable of setting up purulent inflammation. In one of our cases, reported by Bloodgood, Dr. Cushing found gas-bacilli without gas in a small subcutaneous abscess of a stump two

[37] It is to be regretted that in the cases reported by Prutz (Deutsche Zeitschr. f. Chirurg., 1898, XLVII, p. 591), as traumatic entrance of air into the knee joint, no bacteriological examination was made.

months after amputation of the thigh for emphysematous gangrene of the leg, the amputation having been followed by uninterrupted convalescence.

After death there may be rapid extension of the subcutaneous emphysema, and at autopsies made a few hours after death gas-bubbles may be found in the heart, vessels, liver and other organs, but as to this occurrence there is no rule. As I have already explained wide-spread distribution of gas in the blood and organs in early autopsies indicates entrance of the bacilli into the circulation during life.

As is to be expected from the etiology of many of the cases of emphysematous gangrene, emboli of fat and of bone-marrow cells are common in the pulmonary capillaries, but I do not know that in any case they contributed to the fatal result.

The prognosis of emphysematous gangrene is more favorable to-day than before the antiseptic period. The disease terminated fatally in 59 per cent of the cases in my list. In the cases observed and treated at the Johns Hopkins Hospital —10 in number—the fatality was 50 per cent, but of these one was a gaseous phlegmon of the pelvis extending to the thigh, resulting from traumatic rupture of the rectum, a second was a gaseous phlegmon of the abdominal wall following removal of the appendix and complicated with diffuse gangrenous peritonitis, and a third case terminated twenty-five days after disappearance of a gaseous phlegmon of the thigh (treated by incisions) from a late streptococcus infection, gas and the gas-bacillus having disappeared. Of the two remaining fatal cases in one—emphysematous gangrene following compound fracture of the thigh—amputation was refused by the patient until the fourth day when he was in a state of collapse and died fifteen hours later, and in the other —compound fracture of the skull and both lower extremities —the patient died thirty hours after the accident, having never regained consciousness.

When the disease is accessible to surgical treatment, is not complicated by other grave conditions, and is promptly recognized and treated, the prognosis, according to the experience of my surgical colleagues, Professor Halsted and Dr. Bloodgood, is not very unfavorable.

The clinical evidence favors the view that, at least in most uncomplicated fatal cases, death is due to toxæmia. Norris was unable to demonstrate the presence of strong toxins in artificial cultures of Bacillus aërogenes capsulatus, but, as is well known, the same difficulty is encountered with many other pathogenic bacteria which are believed to produce poisons in the human body. Muscatello is also of the opinion that the constitutional symptoms are attributable to toxæmia.

The suggestion that death may be due to gaseous embolism is not new. Pirogoff and other of the older observers knew that gas-bubbles may be found within the heart and vessels very soon after the death of patients from emphysematous gangrene. In the discussion on Langenbeck's paper on traumatic infiltration before the Society of German Military Surgeons in 1870, Senator [58] advocated the supposition that death is caused by gas-embolism. While the possibility of this occurrence as the cause of death may be admitted, there is at present no proof of this opinion. Gas-bubbles are by no means always found in the blood and organs after death from emphysematous gangrene, and the clinical histories of those in whom they are found post mortem do not appear to differ from those where they are absent. In experimental gaseous phlegmons in guinea-pigs there is no evidence of the presence of gas-bubbles in the circulation during life.

In one of our cases (Mann) death resulted from tetanus and Verneuil [59] has reported three cases which without bacteriological examination he, in conformity with current French opinion, calls malignant œdema, where also tetanus intervened. There is nothing surprising in this association when one considers that the home of the tetanus bacillus, like that of the gas-bacillus, is the soil. The period of incubation for tetanus is longer than for infection with the gas-bacillus, the former appearing rarely before the seventh day, and the latter usually within two or three days after the injury.

Prophylactic measures against emphysematous gangrene are sufficiently obvious from the etiological factors which have already been considered. It is important in wounds of the character most frequently followed by this complication to search microscopically and by cultures for Bacillus aërogenes capsulatus. The examination of coverslips, stained by Gram, will usually suffice for a probable diagnosis. I have already cited instances in which this bacillus has been detected before the onset of emphysema and in which there is good reason to think prompt surgical treatment warded off severe infection. The possibility of infection from the intestinal canal, as well as from external sources, is to be borne in mind.

The cases were treated either by free incisions or by amputation or both. The results were better after amputation than after simple incisions. Of the cases of emphysematous gangrene affecting primarily the extremities, the recoveries numbered 68 per cent after amputation, and 33¼ per cent after incision without amputation. Careful study of individual cases shows that amputation is by no means always necessary. Everything depends upon early recognition of the nature of the infection. Dr. Bloodgood,[60] from a relatively large experience, says: "If the infection is recognized early, and the destruction of the soft parts and bone is not extensive, free incisions with immediate continuous bath treatment should be tried. If the general symptoms of infection are not immediately relieved, amputation should be done. If, however, the infection is recognized late one should take no risk but amputate at once. . . . An early diagnosis will probably save life, and from many observations an amputation may not always be necessary."

A similar position as to prognosis and treatment is taken by Muscatello and Gangitano in their valuable paper on gaseous

[58] Deutsche militärärztl. Zeitschr., 1872, I, p. 260.

[59] Semaine méd., 1890, p. 403.

[60] Progressive Medicine, 1899, IV, December, p. 174.

gangrene, in which they also emphasize the value of abundant irrigations with disinfectant and oxidizing solutions. In the service of Dr. Halsted at the Johns Hopkins Hospital the continuous bath treatment has been found useful. Hitschmann and Lindenthal are certainly mistaken in their assertion that incisions are usually without favorable effect and that early amputations offer the only chance of recovery. As pointed out by Thorndike and others recovery may follow amputation even when it is impossible to remove the whole of the diseased tissues.

Gaseous Abscesses.

The presence of gas in closed abscesses may be due to Bacillus aërogenes capsulatus.

It seems to me questionable whether Fraenkel's[a] second case should be classified under emphysematous gangrene. In the region of the right elbow joint there was a painful fluctuating swelling from which on incision fetid pus mixed with gas-bubbles escaped. The subcutaneous tissue was partly necrotic. A similar swelling over the left shoulder joint was also incised. Besides the gas-bacillus, streptococci and long delicate bacilli appeared in the cultures. There is no statement concerning the causation of these abscesses. Passow's case was also a peculiar one. Following a superficial, suppurating wound of the right hand there appeared panophthalmitis with septicæmia, during which a crepitating swelling of the right shoulder and upper arm developed, from which on incision were evacuated gas and a brownish, fetid secretion, but no actual pus. Besides staphylococci a bacillus, believed by Passow to be identical with the gas-bacillus, was cultivated. I have included these two cases under the gaseous phlegmons or emphysematous gangrene, although at least the former seems to have been one of definite abscesses.

Soupault and Guillemot[a] have recorded two cases of gaseous abscess, following hypodermic injections, due to the gas-bacillus. They call the organism "Bacillus perfringens" (Veillon and Zuber), but identify it with Fraenkel's Bacillus phlegmones emphysematosæ. Of the American work on Bacillus aërogenes capsulatus they have apparently never heard. In Soupault and Guillemot's first case a large abscess containing fetid pus and gas with the odor of sulphuretted hydrogen followed the injection of 40 cc. of 5 per cent common salt solution into the thigh of a patient with advanced and rapidly extending pulmonary tuberculosis. The injection, made September 7, was at once followed by a painful swelling of the thigh, over which the skin was reddened; on September 15, gas was detected; on September 25, 300 cc. of chocolate-colored, thick, viscid pus mixed with gas were aspirated, and 8 days later an incision, from which 200 cc. of reddish pus escaped, was made, after which the abscess slowly healed. Aërobic cultures were negative; in anaërobic cultures Bacillus aërogenes capsulatus (Veillon and Zuber's Bacillus perfringens) was obtained in pure culture. From the foul odor of the pus and gas, which is said to have been distinctly that of sulphuretted hydrogen, it is probable that, at least at some stage of the process, other microorganisms were associated with the gas-bacillus, which survived for nearly a month in the abscess.

The same authors report a second case of gaseous abscess, which in this instance followed the injection of artificial serum into the abdominal walls of a child with grave typhoid fever. The abscess, which was opened by thermo-cautery, contained yellowish, viscid, inodorous pus. Three aërobic organisms, of which Staphylococcus aureus predominated, were found associated with Bacillus aërogenes capsulatus.

Soupault and Guillemot describe a third case of a young man, 19 years old, in whom a gangrenous phlegmon with extensive sloughing followed an injury of the left leg received in playing foot-ball. After the critical condition seemed to have passed, an emphysematous subcutaneous swelling appeared in the opposite, healthy leg near the inside of the knee. A hypodermic injection of salt solution had been made in the external part of the right thigh, but the authors do not consider that this had anything to do with the gaseous swelling, as the latter was too remote from the site of injection. They, therefore, attribute the gaseous phlegmon to transportation of bacilli by the circulation from the opposite extremity. Bacillus aërogenes capsulatus was found in pure culture. Recovery was uninterrupted.

Soupault and Guillemot emphasize the benign course of the affection in their three cases, as well as in other instances of gaseous abscess following hypodermic injections which they cite from published records. Conditions favoring the occurrence of such abscesses after these injections are the irritating quality of the fluids injected (ether, tincture of musk, camphor, acid solutions of morphine, concentrated saline solutions, etc.) and lowered general resistance of the patient produced by typhoid fever, tuberculosis, cancer, cholera, hæmorrhages, and other grave diseases. When death occurs, they think that it is usually attributable to the primary disease, not to the infection with the gas-bacillus.

I have included in my statistics of emphysematous gangrene 5 cases of gaseous phlegmon following hypodermic injections, 3 of these (Carroll 2, Dobbin 1) being of normal salt solution in puerperal women, and 2 (E. Fraenkel) being respectively of oil of camphor followed at once by ether in a patient after extirpation of a pyloric cancer, and of a solution in water of sulphuric acid and muriate of morphia in cholera. That the most unirritating of solutions may be followed by gaseous phlegmon is demonstrated by the three cases in which physiological salt solution was injected. Of these latter two died, and one recovered after incision of the phlegmon. Both of Fraenkel's cases terminated fatally.

Including Soupault and Guillemot's 3 instances of gaseous abscess we have altogether 8 cases of gaseous abscess or phlegmon following hypodermic injections of various substances, and caused by Bacillus aërogenes capsulatus, usually in association with other bacteria.

[a] Ueber Gasphlegmonen, p. 15, Hamburg and Leipzig, 1893.

[a] Bull. et mém. Soc. méd. d. hôp. de Paris, 1900, 3. S., XVII, p. 216.

Brieger and Ehrlich's[52] two observations of fatal gaseous phlegmon following the hypodermic injection of tincture of musk in typhoid fever are usually cited as the first instances of authenticated malignant œdema in man, but it cannot be said that the bacillus concerned was proven beyond doubt to be that of malignant œdema, and with our present knowledge of the etiology of this class of affections it is permissible to question the accuracy of the identification of the bacillus in these two cases, notwithstanding the high authority of the observers. In the case of gaseous abscess following the intramuscular injection of ether reported by Bucquet,[53] and in the two similar cases reported by Lauteret,[55] all three ending in recovery, no bacteriological examination was made.

It is evident from the foregoing cases that Bacillus aërogenes capsulatus, in combination usually with pyogenic bacteria, is the chief, if not sole, cause of the gaseous abscesses or emphysematous gangrene which occasionally follow hypodermic injections. Although in none of the cases reported has this bacillus been looked for in the fluids injected, the presumption is that it was present either in them or in the syringe, although there is a possibility of the introduction of this organism from the skin of the patients, and even of its conveyance by the circulation from the intestine to the site of tissues damaged by the injection of irritating substances.

I shall refer subsequently to the occurrence of the gas-bacillus in abscesses without gas and to other manifestations of its pyogenic capacity.

Uterine Infections.

Knowledge of Bacillus aërogenes capsulatus is of not less interest and importance to the obstetrician than to the surgeon. Infection of the puerperal uterus by this microorganism leads to a variety of morbid conditions, some comparatively mild, others of the utmost gravity.

The wide distribution of the gas-bacillus in the intestinal canal and the outer world renders as explicable the occasional presence of this bacillus in the female genital tract as that of the colon bacillus in the same situation. Lindenthal[56] found the gas-bacillus in the vagina without the presence of gas or other pathogenic effects twice out of six puerperal cases examined. According to the observations of others, Lindenthal's experience would seem to be exceptional. As with so many other pathogenic bacteria the mere presence of the organism upon exposed surfaces does not necessarily signify infection.

I shall consider the uterine infections by the gas-bacillus under the headings of emphysema of the fœtus, puerperal endometritis, physometra, emphysema of the uterine wall, and puerperal gas-sepsis, although these conditions may be associated with each other.

Emphysema of the Fœtus.—The occurrence of emphysema in the dead fœtus in utero has been known for centuries,[57] but it was not until 1897, when Dobbin published his paper on "Puerperal Sepsis due to Infection with the Bacillus aërogenes capsulatus"[58] that the cause of this condition was determined to be invasion by Bacillus aërogenes capsulatus. In this case gas and the gas-bacillus were both recognized during the life of the patient in the fœtus, the placenta and the cavity of the uterus, and after death there was general gas-formation throughout the body.

Dr. Dobbin has kindly given me the notes of a second, unpublished case observed by him. He was called to see a woman in difficult labor, upon whom repeated attempts at delivery of a dead fœtus had been made. Upon examination he recognized crepitation of the caput succedaneum while the fœtus was still in utero. Upon delivery the fœtus was emphysematous with foamy organs. The gas bacillus was found in pure culture in the fœtus and mixed with other bacteria in the amniotic fluid. No gas was recognized in the uterus after delivery. The patient made a good recovery without evidence of sepsis.

Menge and Krönig[59] have observed three instances of fœtal infection by the gas-bacillus and have brought strong evidence that usually the invasion is through the mouth of the fœtus, the bacilli being taken into the lungs or stomach by inspiring or swallowing amniotic fluid. In their cases the bacilli were not found in the part of the umbilical cord attached to the placenta, but in Dobbin's first case this as well as the placenta itself was infected with the gas-bacillus. The amniotic fluid within the intact membranes, as is well known, is usually sterile, and only exceptionally becomes infected before rupture of the membranes, so that the infection of the fœtus from this source is generally after this rupture. As shown by Menge and Krönig, all grades of invasion of the fœtus by the gas-bacillus occur, so that there may be only a small amount of gas, and this limited to the lungs or the alimentary canal or both. The medico-legal importance of not mistaking for air this gas in the fœtal lungs produced by gas-bacilli should be emphasized.

As is well known, fœtal emphysema is usually unattended with danger to the mother. In two of the five cases due to Bacillus aërogenes capsulatus in my list the puerperium was even without rise of temperature, in two there was mild fever, but in Dobbin's first case there was rapidly fatal gas-sepsis.

will be considered cases of acute uterine infection with the

Puerperal Endometritis.—Under the heading "gas-sepsis"

[52] Berliner klin. Woch., 1882, XIX, p. 661.

[53] Thèse, Paris, 1883.

[55] Thèse, Paris, 1898.

[56] Wiener klin. Wochenschr., 1897, pp. 3 and 35.

[57] It is usually stated that this condition was known to Celsus, but he does not expressly mention the presence of gas, although this is to be inferred. In the chapter on extraction of the dead fœtus, he says: "Solet etiam evenire, ut is infans humore distendatur, exque eo profluat fœdi odoris sanies." Milligan's "Celsus," p. 394, Edinburg, 1831.

[58] Bulletin of the Johns Hopkins Hospital, 1897, VIII, p. 24.

[59] Bakteriologie des weibl. Genitalkanales, Teil II, p. 167, Leipzig, 1897.

gas-bacillus followed by invasion of the blood and organs by this organism. Here it may be mentioned that Bacillus aërogenes capsulatus may be present in the uterus, usually in association with other bacteria, in both mild and severe cases of puerperal endometritis without the recognition of gas in the fœtus, or the uterine cavity, or wall. An example of such a case is an unpublished one in the service of Dr. J. Whitridge Williams, of which the notes have been furnished me by Dr. Dobbin. A woman with rhachitic pelvis, upon whom delivery by forceps had been attempted before admission to the Johns Hopkins Hospital, was there delivered by craniotomy. There was no gas in the fœtus. Forty-eight hours later Bacillus aërogenes capsulatus, together with streptococci, was found in the uterine lochia. No gas was detected. The patient developed fever, but recovered.

In two cases, one reported by Dobbin[70] and the other by Blumer,[71] the gas-bacillus, although not identified with absolute certainty, was probably present in the puerperal uterus in association with the typhoid bacillus.

Physometra.—Distension of the uterine cavity with gas (physometra or tympany of the uterus) was present in Dobbin's first case, already cited, and is often associated with emphysema of the dead fœtus, but may occur without the latter and even in the non-pregnant uterus. This curious condition was formerly ascribed to entrance of air or to ordinary putrefaction,[72] but it is now known to be the result of the activity of gas-producing bacilli.

Since the observations of Lindenthal,[73] reported in 1898, it cannot be doubted that Bacillus aërogenes capsulatus is the chief cause of physometra. He found this bacillus in five cases during life and reproduced the condition experimentally in guinea-pigs. He is justly skeptical of the correctness of the previous reports of Gebhard[74] concerning the agency of the colon bacillus in generating gas within the uterus. We know from Theobald Smith's investigations that the colon bacillus can produce gas only from carbohydrates, whereas it is the most distinctive biological attribute of our gas-bacillus that it can produce gas from proteids. Until it has been shown that the amniotic fluid and uterine contents may under any conditions contain enough carbohydrate to explain the development of gas by the colon bacillus there is every reason to question the claims for this bacillus as a cause of tympany of the uterus.[75]

My list of cases contains 10 instances of physometra in which Bacillus aërogenes capsulatus was demonstrated. Although as some of our cases show, this condition may be associated with invasion of the bacilli into the wall of the uterus and by acute gas-sepsis, these occurrences are exceptional and the prognosis is in general a favorable one. Most of the cases furnish a good illustration of the resistance of living human tissues to the action of the gas-bacillus. Doubtless in these cases the bacilli grow simply in the amniotic fluid after rupture of the membranes, and in the dead fœtus, these offering no vital resistance, whereas we must suppose that the intact uterine wall offers ordinarily an effective resistance to the invasion and multiplication of the gas-bacillus. That occasionally the bacilli may find other dead material in the uterus, as in sloughing myomata and cancers, is evident from the histories of some cases of physometra.

Emphysema of the Uterine Wall.—Far graver in significance is septic emphysema of the uterine wall, of which Halban[76] has recently reported an interesting case due to Bacillus aërogenes capsulatus. Graham, Steward and Baldwin and P. Ernst were the first to demonstrate this bacillus in this condition, their papers, to which reference has already been made, appearing simultaneously in August, 1893. Eleven instances of emphysema of the wall of the uterus, all puerperal, have been reported, of which 5 were recognized during life. In all but Halban's case there was also physometra, and this would seem to be a necessary accompaniment unless the cervical canal is open so as to permit the escape of the gas from the uterine cavity. All of the cases were fatal, and in most gas was found at autopsy in the blood and internal organs.

Subperitoneal emphysema is a condition which has been observed after rupture of the uterus, Dischler[77] having collected reports of 14 cases. In most instances this has been attributed to entrance of air, but I think that it is safe to predict that the gas-bacillus will be found in similar cases in the future, if proper methods for its detection are employed. I know, however, of no instance of this condition in which it has been looked for.

Puerperal Gas-Sepsis.—I have adopted from Halban the term "gas-sepsis" as a convenient one—although, perhaps, open to criticism—to designate the important group of fatal puerperal cases in which gas-bubbles are found at early autopsies in the heart and vessels and often also in the organs and tissues under conditions where we must suppose that gas-bacilli and possibly gas have passed from the uterus into the circulation during life.[78] Here in my opinion belong most of the cases which have been reported as deaths due to the entrance of air into the uterine veins. This opinion which I expressed in my first communications on the gas-bacillus in 1891 and 1892, received prompt confirmation in the papers

[70] Am. Journ. Obstetrics, 1898, XXXVIII, p. 185.

[71] Ibid., 1899, XXXIX, p. 42.

[72] The older hypotheses and records on physometra and emphysema of the fœtus are fully presented by Staude, Zeitschr. f. Geb. u. Gynäk., 1878, III, p. 191.

[73] Monatsschr. f. Geb. u. Gynäk., 1898, VII, p. 269.

[74] Zeitschr. f. Geb. u. Gynäk., 1893, XXVI, p. 480, and 1897, XXXVII, p. 132.

[75] Halban (Monatsschr. f. Geb. u. Gynäk., 1900, XI, p. 102) states that he has found lactose once in the amniotic fluid of a normal puerpera. Further studies of this subject are needed.

[76] Monatsschr. f. Geb. u. Gynäk., 1900, XI, p. 88.

[77] Arch. f. Gynäk., 1898, LVI, p. 199.

[78] Gas-sepsis in this sense occurs also in other than uterine infections with the gas-bacillus.

of Graham, Steward and Baldwin and of P. Ernst in August, 1893, and has since been strengthened by other similar observations. Cases described by Wendeler[79] as sepsis acutissima belong also in the same category.

My list includes 13 puerperal cases in which gas-bubbles and the gas-bacillus were found at autopsy in the blood or organs; but in only 7 of these does it seem to me conclusive or extremely probable that the infection occurred during life.[80]

The most remarkable of these cases is that reported by Graham, Steward and Baldwin of a woman, upon whom abortion had been recently produced, who during the four hours immediately preceding death became emphysematous over nearly the whole body. At the autopsy gas and gas-bacilli were found everywhere throughout the body. In Dalton and Bremer's[81] case, also one of criminal abortion, an emphysematous swelling of the arm and pectoral region was likewise recognized during life. These cases are of importance as demonstrating the invasion of the body by the gas-bacillus from the uterus while the blood is still circulating. In Halban's and Dobbin's cases gas was also recognized during life within the wall or cavity of the uterus.

In the majority of cases of puerperal gas-sepsis there has been some operative interference preceding infection, such as criminal abortion, forced delivery for placenta prævia or other causes, or the manipulations of an unskilled midwife. The fulminating character of the infection, death being sometimes very sudden, is a notable feature of many of the cases.

In a case of attempted criminal abortion reported by Perkins[82] the patient, according to the statement of the practitioner in whose office death occurred, died suddenly, and at the autopsy twelve hours later in cold weather, gas was found in the vena cava, heart, and other vessels, with evidences of injury to the pregnant uterus. The case was reported by Perkins as one of death from air-embolism, and certainly with as much and even more plausibility than most cases thus reported. After the publication, Dr. Perkins, upon the request of Dr. Dobbin, was so good as to send the uterus, well preserved in alcohol, to my laboratory where Dr. Dobbin demonstrated in the uterine vessels and tissue bacilli morphologically and in staining reaction identical with Bacillus aërogenes capsulatus.[83]

I would not be understood to deny the possibility of the occurrence of fatal air-embolism from the uterus. A very few of the reported cases are difficult to interpret upon any other supposition, but I do claim that the foundations of this doctrine have been seriously shaken by our discovery and investigations of the gas-bacillus, and that no case, however plausible, can be considered as positively proven without a satisfactory bacteriological examination. The limitation of gas to the right heart and adjacent vessels may occur from invasion by the gas-bacillus, and is not, as often represented, peculiar to air-embolism. Did we not know how long it takes new knowledge, especially that originating in this country, to penetrate throughout the medical world, it would be amazing that cases should still continue to be reported, as they are,[84] of deaths ascribed to air-embolism without any bacteriological examination or even any reference to the possibility of any other explanation. I am not aware that in any instance of alleged air-embolism, a bacteriological examination has been made, which would exclude the presence of gas-forming bacteria.

Whether, as suggested by Staude, in any of the cases with gas within the uterine cavity, death is attributable to gaseous embolism, is, I think, an open question. It is possible, although I know of no proof of it, that in some of the cases of sudden death during or immediately after some manipulation or operation on the pregnant uterus and attributed to air-embolism, gas, generated by bacteria, may have existed under pressure within the uterine cavity and have entered wounded veins in sufficient amount and so suddenly as to have caused death.

To what extent the free gas found in the blood-vessels, heart and internal organs, even very soon after death from what has been described as puerperal gas-sepsis, is there during life, is a question difficult to answer. I have already considered this subject, and in this connection shall again emphasize the importance of caution in interpreting the presence of gas in these situations as a vital phenomenon, although there is evidence that it may be such.

Infections of the Urinary Tract.

There is evidence that the urinary tract may not only be a portal of entrance for the gas-bacillus into the circulation or adjacent tissues but also be itself the seat of infection by this organism. Unfortunately for the decisive interpretation of many of these cases, Bacillus aërogenes capsulatus has, so far as I am aware, hitherto been found in the urinary tract only after death, although in some instances so soon thereafter and under such conditions that its presence during life cannot be doubted.

I have already called attention to instances of emphysematous gangrene following external urethrotomy and other operations on the urinary passages.

[79] Monatsschr. f. Geb. u. Gynäk., 1896, IV, p. 581.

[80] These are the cases reported by Graham, Steward and Baldwin, P. Ernst, Menge and Krönig, Dobbin, F. C. Wood (Med. Record, Apr. 15, 1899), Cesaris-Demel, and Halban, to whose papers references have already been given.

[81] Am. Journ. Med. Sc., 1888, XCV, p. 594. This infection, although attributed to the bacillus of malignant œdema, was probably due to the gas-bacillus.

[82] Boston Med. and Surg. Journ., 1897, CXXXVI, p. 154.

[83] Dobbin has reported the results of his examination with further notes of this case in the Monatsschr. f. Geb. u. Gynäk 1897, VI, p. 375.

[84] Zorn (Münch. med. Woch., 1898, p. 567) may be cited as an example. Hübl (Wiener klin. Woch., 1900, XII, p. 111) has also recently reported two instances of alleged air-embolism—placenta prævia—without any bacteriological examination. He assumes incorrectly that the distribution of the gas at autopsy is a decisive point as between air-embolism and gas-sepsis.

Among the cases of general invasion of the blood and organs (foamy organs) by the gas-bacillus observed by myself and others are several in which the portal of entry was the urethra, bladder or other part of the urinary tract.[85] In a case of urethral stricture with cystitis, for which perineal section had been done, reported by Welch and Flexner, gas-bacilli were found *three-quarters of an hour after death* in large numbers in the bladder, ureters and renal pelvis, and a few gas-bubbles and gas-bacilli were already present in the blood of the right ventricle. In Howard's case of meningitis caused by the gas-bacillus, to be cited subsequently, he considers that the portal of entry was the urinary tract.

Gas, generated by Bacillus aërogenes capsulatus, has been found in the urinary passages in 6 cases which have come to my notice.[86] The gas may be either free in the cavity of the bladder, ureters or renal pelvis, or contained within submucous blebs, or in both situations.

Welch and Flexner[87] have reported an instance of pneumaturia in a diabetic man in whom, six hours after death, without trace of cadaveric decomposition, the urinary bladder was found filled with frothy urine containing Bacillus aërogenes capsulatus in pure culture. This case indicates that the colon bacillus and Bacillus lactis aërogenes are not the sole causes of pneumaturia in diabetics. Dr. Flexner has given me the notes of a second case of pneumaturia upon which he made the autopsy at the University Hospital, Philadelphia. This was of a patient with chronic cardiac disease who had been catheterized twenty-eight hours before admission and who died thirty hours after admission. At the autopsy, made one hour and a half after death, about 60 cc. of frothy urine were found in the bladder from which Bacillus aërogenes capsulatus, together with Staphylococcus aureus and Streptococcus pyogenes (no colon bacilli), was cultivated. Neither gas nor gas-bacilli were found elsewhere in the body. The mucous membrane of the bladder was œdematous. There can be little doubt that in this case the gas-bacillus was introduced by the catheter into the bladder.

In one of Welch and Flexner's cases (Case XVIII) of hypertrophied prostate with pyoureter and pyonephrosis, the renal pelves and ureters were found at autopsy distended with gas and containing pus mixed with bubbles of gas. Small gas-cysts were present in the mucous membrane of the renal pelves. Neither gas nor gas-bacilli were present outside of the urinary organs. In this case cocci and colon bacilli were associated with the gas-bacillus.

In a case of Dr. Kelly's, of which the full records have been given me by Dr. Miller,[88] there was pneumaturia demonstrated by cystoscopic examination and ureteral catheterization to come exclusively from the inflamed left renal pelvis and ureter. Among cocci and other bacteria were found on coverslips bacilli morphologically resembling Bacillus aërogenes capsulatus, but unfortunately no anaërobic cultures were made. None of the bacteria which grew aërobically produced gas in lactose-agar. This case is interesting as demonstrating that the gas may come exclusively from one renal pelvis and ureter, but the microorganism producing the gas was not satisfactorily demonstrated. It seems certain that it was an anaërobic organism, and from the microscopical appearances may have been the gas-bacillus.

The subject of submucous gas-cysts will be considered subsequently; but here it may be mentioned that besides the gas-cysts in the renal pelves noted by Welch and Flexner in the case already cited, Goebel found gas-blebs, containing in pure culture Bacillus aërogenes capsulatus, beneath the mucous membrane of the urinary bladder, without gas elsewhere in the body, and Dunham has reported a like condition of the bladder in a case of emphysematous gangrene with general invasion of the blood and organs by the gas-bacillus.

Bacteria have been found in emphysema of the bladder (cystitis emphysematosa) also by Eisenlohr,[89] Camargo,[90] and Kedrowsky,[91] but it is impossible from the authors' descriptions to identify their bacteria. Kedrowsky considers that the bacillus isolated by him is allied to Bacillus aërogenes capsulatus, but less sensitive to oxygen. Perhaps it was Sanfelice's Bacillus pseudo-œdematis maligni, to which I have already referred, but Kedrowsky's description of his cultures hardly inspires confidence in their purity.

Welch and Flexner and Howard have reported finding the gas-bacillus, in association with other bacteria, in inflammatory lesions of the bladder, renal pelvis and kidneys, without the detection of gas. Howard considers that in one of his cases the bacillus was concerned in the etiology of suppurative lesions of the kidneys but in this case the colon bacillus and Streptococcus pyogenes were also present.

Infections Derived from the Gastro-Intestinal Canal.

Mention has already been made of the frequent, if not constant, presence of Bacillus aërogenes capsulatus in the intestinal canal, of gaseous phlegmons originating from this source, and of the readiness with which intestinal bacteria may gain access to the genito-urinary tract.

The intestine is by far the commonest source of the gas-bacilli found together with gas-bubbles in the blood and organs at autopsies. This invasion may occur either with or without definite intestinal lesions, and is probably in the majority of cases an agonal or post-mortem event. The mode of distribution and spread of the bacilli in these cases has

[85] Such cases are reported by Welch and Flexner, Goebel, Dunham and Howard in papers already cited.

[86] These do not include some instances of very extensive post-mortem emphysema of the organs with gas everywhere throughout the body.

[87] Case XIII of our list in Journal of Experimental Medicine, 1896.

[88] This case is briefly reported by Kelly and MacCallum, Journ. Amer. Med. Assoc., 1898, XXXI, p. 376, whose paper may be consulted for the full literature of pneumaturia.

[89] Ziegler's Beitr., 1888, III, p. 101.

[90] Thèse de Genève, 1891.

[91] Centralbl. f. allg. Path. u. path. Anat., 1898, IX, p. 817.

been well described by Howard,[92] whose experience has been exceptionally large with this class of affections. Especially demonstrative of invasion of gas-bacilli from the intestine, usually post mortem, is the occurrence of gas-bubbles limited to the neighborhood of the intestine, as in the intestinal wall, within the portal or mesenteric veins, or lymphatics, in the subperitoneal tissues, mesentery and omenta, around the pancreas, in the mesenteric gland, and especially in the loose tissue near the gall-bladder and in the porta of the liver, without gas in more remote situations. I have seen examples of each of these occurrences in very early autopsies without ordinary cadaveric decomposition.

Local Gastro-intestinal Lesions.—Interstitial emphysema of the gastro-intestinal wall will be considered subsequently.

Howard has described several cases with larger or smaller areas of superficial necrosis of the mucous membrane of the stomach and intestine, in which gas-bacilli were present in large numbers. These areas, which may occur either with or without gas-cysts, are found most frequently beneath the folds of the valvulæ conniventes and are characterized by absence of nuclear staining and disintegration of the cells and tissue, usually without marked inflammatory reaction.

Bacillus aërogenes capsulatus may undoubtedly be a cause of meteorism. Instances of this are reported by Welch and Flexner and by Howard.

Pneumo-peritonitis with and without Perforation.—My records include 13 cases of diffuse peritonitis in the exudate of which Bacillus aërogenes capsulatus was found. Eleven of these were in autopsies made either by Dr. Flexner or myself, 7 having already been published by us in 1896. The remaining 2 cases (both being perforations of gastric ulcers) have been reported by Page,[93] and by Pratt and Fulton.[94] It was the observation of these cases which first called my attention to the frequent presence of the gas-bacillus in the intestine.

Ten of the cases were perforative and 3 were non-perforative. Of the former 4 were the result of perforation of typhoid ulcers, 4 of gastric ulcers,[95] one of strangulated, gangrenous intestine and one of a cancerous ulcer of the duodenum. In the last case (autopsy fourteen hours after death) the exudate was sero-fibrinous and the gas-bacillus was found in pure culture[96] and abundantly in the peritoneal cavity and was absent from other organs and the blood. In the other perforative cases the gas-bacillus was mixed with other bacteria, although in some instances it predominated. In all of the cases the abdomen was greatly distended with gas and usually there was great tympanites.

I attach especial importance to the case fully reported by Welch and Flexner,[97] in which we brought conclusive evidence of the occurrence of pneumoperitonitis without perforation, the first of the kind on record in which similar proof was obtained. The presence of gas in the peritoneal cavity was recognized during life. Since our publication a similar case has been observed by Dr. Flexner in Manila, who has kindly furnished me the notes. At the autopsy, twelve hours after death, there was found hæmorrhagic infarction of the lower part of the ileum and adjacent part of the large intestine, caused by the passage of this part of the intestine through a hole in the mesentery. The peritoneal cavity was greatly distended with gas which burnt with a pale, blue flame. There was a large amount of frothy, bloody serum in the peritoneal cavity together with a fibrinous exudate. The most careful examination showed no perforation. Bacillus aërogenes capsulatus was obtained in pure culture and abundantly from the peritoneal fluid. Gas was absent from the blood and other organs.

We have found the gas-bacillus, mixed with other bacteria, twice in circumscribed, gas-containing, intraperitoneal abscesses resulting from perforation of the appendix vermiformis.

Hepatic and Biliary Infections.—The development of gas in the liver is so striking a phenomenon in most autopsies where the gas-bacillus and free gas are found in the blood and organs that P. Ernst used the term "Schaumleber" for the title of his article on the gas-bacillus, published a year after the paper by Welch and Nuttall, in which we first directed attention to the subject of foamy organs and the gas-bacillus.[98] I have already considered the general subject of gas-bubbles in the blood and organs, and wish here to call attention especially to infections of the gall-bladder and biliary passages by Bacillus aërogenes capsulatus.

In cases of foamy liver gas may be found in the bile-ducts and gall-bladder, but my experience is that, when the gas-bacilli reach the liver through the blood-vessels, the appearance of gas in these situations is a rather late occurrence and met chiefly in advanced cases. In contrast to these cases are the observations of gas in the biliary passages, associated sometimes with definite lesions of the bile-ducts and liver, where the evidence is that the gas-bacilli entered from the

[92] Op. cit., p. 491.

[93] Canada Lancet, May, 1900.

[94] Boston Med. and Surg. Journ., June 7, 1900, p. 599.

[95] Welch and Flexner have reported an instance of peritonitis from perforated gastric ulcer in a rabbit, in which the gas bacillus was found.

[96] The purity of the culture in this case is explicable by the results of Cushing and Livingood's interesting bacteriological and experimental studies of the duodenal flora published in Contributions to the Science of Medicine, Dedicated by his pupils to William Henry Welch on the 25th Anniversary of his Doctorate, p. 543, Baltimore, 1900.

[97] Op. cit., p. 35.

[98] Heydenreich's paper on "Emphysem der Leber" (Centralbl. f. Bakter., 1897, XXI, p. 305) may be mentioned as a curiosity. He had never heard of the gas-bacillus or of any other investigation of the subject later than 1872. In contrast to this is the interesting article of P. Bernhardt on pneumathæmia and foamy organs with full consideration of the recent literature. Deutsche med. Woch., 1900, p. 83.

intestine directly into these passages. Two such cases have been reported by Howard,[99] and I have observed two cases.

Pratt and Fulton [100] report a remarkable case of cancer of the common bile-duct and pancreas in which cholecystotomy was performed, the edges of opening in the gall-bladder being stitched to the abdominal walls. At the autopsy the liver was found studded with minute abscesses with greenish translucent walls. In coverslips, sections and cultures Bacillus aërogenes capsulatus was found in pure culture in these small biliary abscesses, but there was no gas in the abscesses, the liver, blood, or other organs. A somewhat similar case, in which cholecystenterostomy for gall-stones had been performed, was previously reported by Nicholls [101] from Adami's laboratory. Here also multiple miliary abscesses containing the gas-bacillus were found in the liver, but in this case gas was present in the liver, as well as in the blood and other organs, the autopsy being six hours after death. Larkin [102] has likewise reported a case of hæmorrhagic pancreatitis with fat necroses and small, multiple hepatic abscesses with gas-holes in the liver, from which Bacillus aërogenes capsulatus was isolated. The autopsy was eight hours after death.

Hintze [103] has recorded a post-mortem observation of gas in the inflamed bile-ducts with cholelithiasis. He cultivated only the colon bacillus, but it does not appear that he made anaërobic cultures.

From the foregoing cases it is to be inferred that the gas-bacillus may invade the bile-ducts and gall-bladder from the intestine, and sometimes during life, and that it may not only produce gas but also necroses and purulent inflammation. The presence of gall-stones, cancer of the bile-ducts and operations on the gall-bladder favor this mode of infection.

Rist [104] found the gas-bacillus (Bacillus perfringens), without gas or other lesion attributed to it, in an extirpated gall-bladder containing a calculus and clear viscid fluid.

Interstitial Emphysema of the Gastro-Intestinal, Genito-Urinary and Biliary Tracts.

One of the most interesting lesions produced by Bacillus aërogenes capsulatus is the formation of submucous or subserous gas-cysts or blebs, of which the earliest examples attributed to this organism were reported by P. Ernst, Goebel, and Welch and Flexner. They are sufficiently common to have been observed by nearly all investigators who have had much experience with the gas-bacillus in human beings. My list of cases includes 25 instances of this condition, of which 5 were of the stomach, 11 of the intestine (far oftener of the small than the large intestine), 5 of the gall-bladder and bile-ducts, 3 of the urinary bladder, 1 of the renal pelvis, and 1 of the vagina. The majority of the cases were observed by Flexner, Howard, and myself, and in all the gas-bacillus was demonstrated. The case of emphysema of the vagina was reported by Lindenthal.[105]

These gas-cysts vary in size from microscopic dimensions to large blebs. They are most common in the submucous coat, but may be present in the mucous membrane, the muscular coat or beneath the serous covering, in fact, in any part of the membranous wall. They may be few or in enormous numbers, in groups or scattered. In one of our cases the whole small intestine from the duodenum to the ileocæcal valve was studded with small gas-cysts. Gas-cysts of the same general character may be found in the mesentery and omenta.

These gas-cysts are in their inception simply such gas-holes as we are already familiar with in the liver and other organs in cases of local or general invasion with the gas-bacillus. They indicate a foamy or emphysematous condition of the walls of the stomach, intestine, gall-bladder, bile-ducts, urinary bladder and vagina, due to the invasion into these parts of the gas-bacillus.

The condition of the walls of the blebs and of the surrounding tissues varies. Some of the cavities are round and their walls smooth, others are irregular in shape and have ragged walls. They may correspond to dilated lymphatics, but more frequently they do not represent dilatation of any performed channels. There may be communication between adjacent cavities, but oftener the cysts are distinct from each other. The tissue in the immediate neighborhood of the cavities may present no alteration not explicable by the mechanical pressure of the gas, or it may show necrosis in varying degree and extent. Inflammatory changes or cellular reaction which could be reasonably referred to the presence of the cysts or of the gas-bacilli causing them were not noted. Sometimes a little coagulated, homogeneous or granular material is present in sections of the cysts in hardened tissues, as indeed may often be found in gas-holes in the organs.

In sections stained by Gram there is usually no difficulty in demonstrating the relation of the gas-bacilli to the cysts. The bacilli may be in masses in the walls of the cysts, but sometimes they are not more numerous there than in the tissue at a distance from the gas-blebs, and occasionally it requires some searching to find them. By anaërobic methods the gas-bacillus can be cultivated from the cysts or the adjacent tissue.

All of the instances of submucous and subserous gas-cysts in my list were observed post mortem. In the larger number of cases gas-bacilli and gas-bubbles were more or less widely distributed in the blood and organs, but without evidences of ordinary post-mortem decomposition. There are, however, several cases in which these gas-cysts in various situations were the sole manifestation of the presence of the gas-bacillus in the body. Howard has shown that if careful, systematic

[99] Contributions to the Science of Medicine, Dedicated by his pupils to William Henry Welch on the 25th Anniversary of his Doctorate, pp. 475 and 476, Baltimore, 1900.

[100] Boston Med. and Surg. Journ., June 7, 1900, p. 599.

[101] Brit. Med. Journ., 1897, II, p. 1844.

[102] Med. Record, 1898, LIII, p. 354.

[103] Münch. med. Woch., 1895, XLIII, p. 209.

[104] Thèse, Paris, 1898.

[105] Wiener klin. Woch., 1897, pp. 3 and 35.

search is made for areas of necrosis and minute gas-cysts due to Bacillus aërogenes capsulatus in the stomach and intestine, these lesions can be found much more frequently than has been supposed.

It is, with our present information, a difficult matter to say in how many of these cases the emphysematous state existed before death. It is certain that, at least in the great majority of cases in my list, the emphysema was not the result of ordinary post-mortem decomposition. In a large number of the cases the autopsy was made within a few hours after death. Howard, in one of his cases of gas-cysts, limited to the intestine, made the autopsy one hour after death. I have already emphasized the importance of great caution in interpreting as vital processes the various gaseous conditions of parts and organs not open to inspection during life, even when autopsies are made soon after death and there is entire absence of putrefaction, and I can only repeat this caution here. Mere absence of nuclear staining around gas-holes I do not regard as proof of their origin during life.

It would lead altogether too far to enter here into a discussion of the general subject of submucous gas-cysts concerning which there is a large literature, the principal references to which will be found in the articles of Eisenlohr,[106] Camargo,[107] Winands,[108] Orlandi,[108a] Dupraz[109] and Lindenthal.[110] It would appear from a study of the records of the subject that anatomically different conditions have been described under the designation "gas-cysts" (cystides aërifere). Some have been apparently of long standing and show chronic inflammatory changes in the walls of the cysts and the surrounding tissues. The most voluminous records relate to the gas-cysts of the vagina (kolpohyperplasia cystica of Winckel, emphysema vaginæ of Eppinger).

At present we have no warrant to identify the more chronic gas-cysts with thickened walls with the more acute emphysematous condition which I have described as referable to Bacillus aërogenes capsulatus. Nevertheless the former are probably of bacterial origin also, although I am unable to accept the bacteriological findings of Eisenlohr, Camargo, Orlandi and Dupraz as at all convincing, for they made no use of anaërobic methods of cultivation. It is quite possible that Bacillus aërogenes capsulatus is concerned also in the etiology of the gas-cysts of long standing; certainly it is important to apply hereafter anaërobic cultural methods to their study. Lindenthal has no hesitation in identifying the emphysema of the vagina observed by him post mortem and from which in a single case he cultivated what he chooses to call Bacillus emphysematis vaginæ (in reality our Bacillus aërogenes capsulatus) with Winckel's kolpohyperplasia cystica, but, while he may be correct, further observations are needed before their anatomical and etiological identification can be accepted.

The only instance in which gas-cysts of the human intestine have been recognized during the life of the patient is reported by Hahn,[111] who found them in large number upon opening the abdomen. It is to be regretted that no thorough bacteriological examination of this case was made.

In my original communication on the gas-bacillus I ventured the surmise that the bacillus found by E. Fraenkel[112] in hardened sections from a case of gastritis emphysematosa might be identical with Bacillus aërogenes capsulatus, and this suspicion has gained in probability by Goebel's statements based upon a re-examination of the sections, his work having been done under Fraenkel's supervision.

Notwithstanding an effort at compression, so much space has been occupied in the presentation of the foregoing subdivisions of our subject, which in less than a decade has grown to considerable magnitude, that I shall only summarize very briefly a few remaining topics, although all deserve fuller treatment.

Pulmonary and Pleural Infections.—To the two instances of invasion of the lungs by the gas-bacillus reported by Welch and Flexner, I can add the cultivation of this organism from a gangrenous lung by Dr. Flexner in my laboratory. It has been found also by Guillemot[113] and Rist[114] in pulmonary gangrene.

Of much importance is Levy's[115] demonstration of Bacillus aërogenes capsulatus as a cause of pneumothorax without perforation. This case and those of pneumoperitonitis without perforation to which I have already referred have settled affirmatively the long standing controversy concerning the possibility of the generation of gas within closed serous sacs during life. Nicholls[116] has reported an instance of pneumothorax and pneumopericardium without perforation in which the gas-bacillus was probably present. Rendu and Rist[117] also isolated the gas-bacillus (Bacillus perfringens) in a case of putrid pleurisy with gas. May and Gebhart[118] and Finley[119] attribute their two cases of pneumothorax without perforation to the colon bacillus, but in neither were anaërobic cultures made. It is important that in all gaseous affections anaërobes should be searched for.

Bacillus Aërogenes Capsulatus in the Blood during Life.—

[106] Ziegler's Beiträge, 1888, III, p. 101.

[107] Thèse de Genève, 1891.

[108] Ziegler's Beiträge, 1895, XVII,, p. 38.

[108a] Gazz. med. di Torino, 1896, XLVII, p. 781.

[109] Arch. de méd. expér., 1897, IX, p. 282.

[110] Wiener klin. Wochenschr., 1897, pp. 3 and 35.

[111] Deutsche med. Woch., 1899, p. 657.

[112] Virchow's Archiv, 1889, CXVIII, p. 526.

[113] Thèse, Paris, 1899.

[114] Thèse, Paris, 1898.

[115] Arch. f. exp. Path. u. Pharm., 1895, XXXV, p. 335.

[116] Loc. cit.

[117] Bull. et mém. Soc. méd. d. hôp. de Paris, 1899, 3. S., XVI, p. 133.

[118] Deutsches Arch. f. klin. Med., 1898, LXI, p. 323.

[119] Philadelphia Monthly Med. Journ., 1899, I, p. 569.

Exiremely interesting is the demonstration by Gwyn,[120] both by coverslip specimens and by cultures, on repeated examinations, of Bacillus aërogenes capsulatus during life in the blood of a patient, in the Johns Hopkins Hospital, with chorea insaniens and acute endocarditis. I had the opportunity of examining his cultures, which were entirely typical. The patient died but unfortunately no autopsy could be obtained. There was no evidence during life of free gas in the blood or tissues. The case is of importance as demonstrating that gas-bacilli may be in the circulating blood for days in sufficient number to be demonstrable both microscopically and culturally without evidence of free gas. I have already expressed my suspicion that Achalme's anaërobic bacillus, which has likewise been cultivated from the blood, as well as from the tissues, of several cases of acute articular rheumatism, is identical with Bacillus aërogenes capsulatus.

Presence of Bacillus Aërogenes Capsulatus without Gas.—In this connection I may say that the gas-bacillus may be present and even multiplying within the human body without the production of gas. Certain organs, above all the liver, offer much more favorable pabulum for the generation of gas than do others, but even in the liver the bacilli may be present without gas. I have found gas-bacilli in clumps within the spleen and kidney, surrounded by areas of necrosis, without recognizable gas.[120a] I have already cited the demonstrations by Cushing and by Pratt and Fulton of the gas-bacillus in small abscesses without gas, the observation of the latter being particularly complete and satisfactory. Rist [121] has cultivated the gas-bacillus (Bacillus perfringens) from cases of fetid otorrhœa and of mastoid abscess. He does not mention the presence of gas in these cases. I have already cited his isolation of this bacillus from the gall-bladder which contained no gas.

Dr. Harris in my laboratory isolated the gas-bacillus in pure culture from an abscess containing blood and pus in the neck of a dog, following an operation on the jugular vein. There was no gas in the abscess. Aërobic cultures were entirely negative. These observations, however, are not the only ones demonstrating that the gas-bacillus may under certain circumstances and in certain situations manifest pyogenic capacity.

Meningitis. Pyogenic Capacity of Bacillus Aërogenes Capsulatus.—Howard,[122] in April, 1899, reported a case of acute fibrino-purulent meningitis, following operation for urethro-perineal fistula. Bacillus aërogenes capsulatus was found in pure culture in the meningeal exudate. Likewise Hitschmann and Lindenthal [123] have recorded another convincing example of acute cerebral meningitis, following fracture of the occipital bone, in which the gas-bacillus was found unmixed with other bacteria. These authors call attention to the pyogenic power of the gas-bacillus when it attacks the meninges, but, as already shown, the same power may be manifested elsewhere.

Cavities in the Brain.—Finally I would call attention to Reuling and Herring's [124] and Howard's studies of cavities in the brain produced by Bacillus aërogenes capsulatus and to the light which their observations shed upon certain obscure examples of cerebral cavities previously reported.

In this excursion into pneumato-pathology I have invited you to the survey of fields comparatively new and little trodden. I can only hope that our journey has been not without some interest and some profit to you. To me the opportunity to present before such a body as the Massachusetts Medical Society the results of these investigations is one which I highly appreciate.

I desire in closing to pay my tribute of respect and to call to your grateful remembrance the founder of this lectureship, Dr. George Cheyne Shattuck. That the subject of this address would not have been without interest to him may be inferred from the title of his first Boylston Prize dissertation on the theme propounded in 1806 and entitled: "The difference between mortification produced by an external cause and that which is produced by a constitutional defect, the diagnosticks and proper mode of treatment of each." [125] By his noble character, professional services and liberality Dr. Shattuck deserved well of the medical profession of his city and state, and, indeed, of the whole country, and his memory is worthily perpetuated not only by the foundation of this lectureship but also by the endowment of the chair of morbid anatomy in the Harvard Medical School.

[120] Bulletin of the Johns Hopkins Hospital, 1899, X, p. 134.

[120a] Cesaris-Demel's (loc. cit.) opinion that generation of gas in the tissues is merely a putrefactive process pertaining not to any particular kind of microorganism but to irreparable necrosis or damage of the tissues, whereby they become the prey of indifferent gas-producing bacteria, is not proven by his own observations and is opposed by many facts described in this paper.

[121] Thèse, Paris, 1898.

[122] Bulletin of the Johns Hopkins Hospital, 1899, X, p. 66.

[123] Op. cit.

[124] Bulletin of the Johns Hopkins Hospital, 1899, X, p. 62.

[125] Published in Boston in 1808.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

Volume XI is now in progress. The subscription price is $1.00 per year. The set of ten volumes will be sold for $20.00.

ON THE HISTOLOGY OF THE ISLANDS OF LANGERHANS OF THE PANCREAS.

BY EUGENE L. OPIE, M. D.,

Instructor in Pathology, Johns Hopkins University.

The pancreas is much more complex in structure than the other glandular organs which it closely resembles. Langerhans,[1] in an inaugural dissertation published in 1869, gave the first careful description of its histology and showed that the organ has not the relatively simple structure of the salivary glands.

Langerhans studied the pancreas of rabbits which in its essential features does not differ from that of other mammals. The larger ducts are lined by epithelium composed of a single layer of high columnar cells. As the branches of the duct become smaller, the epithelial cells become lower, cubical, and finally flat or, as seen in section, spindle shaped, the nucleus occupying the thicker central portion. The smallest ducts end in the acini composed of high columnar characteristically glandular cells containing next the lumen numerous zymogen granules. Within almost every acinus in contact with the secreting cells Langerhans found one, two, or more cells of a different nature, and to these he gave the name centro acinar cells. They closely resemble the flat spindle-shaped cells lining the very small ducts and he thinks that the epithelium of the duct is continued over the secreting cells into the lumen of the acinus, but he admits that he is unable to determine with exactness the method by which the duct ends.

Distributed at intervals in the parenchyma are groups of cells differing markedly from those of the ordinary glandular type. Such groups are usually round and in tissue, treated two or three days with Müller's fluid, appear with low magnification, as intensely yellow specks. With high magnification they are found to be composed of small, irregularly polygonal cells with a round nucleus and a refractive homogeneous cell body. Of the nature of these cell groups Langerhans declares himself entirely ignorant.

Numerous observers have described these structures which are usually designated islands of Langerhans. Renaut,[2] regarding them as analogous to lymph follicles, speaks of them as "points folliculaires." Podwyssotski[3] calls them pseudofollicles. They have been designated secondary cell groups, inter-alveolar cell islets, etc.

In injected specimens Kühne and Lea[4] found scattered through the organ glomerular structures composed of dilated and tortuous capillaries and showed that these glomeruli correspond to the cell groups which Langerhans described. The islands are penetrated by numerous wide tortuous capillaries which lie between cells forming irregular anastomosing columns. Material injected into the duct of the gland does not penetrate the islands.

Interacinar cell islets have been studied by Harris and Gow,[5] and recently by Diamare,[6] in a great variety of animal species, including mammals, birds, amphibia and reptiles.

Laguesse[7] has studied the development of these bodies in sheep embryos and has reached conclusions which have not, I believe, been confirmed. He finds that at an early period of growth the pancreas is composed of tortuous tubules formed by a single layer of epithelial cells. Here and there occur cells which stain more deeply than those about them and, like the border cells of the stomach, are situated near the outer surface of the tubule. These cells proliferate and form what he calls primary islands of Langerhans. Accepting the observations of Lewaschew, to be mentioned later, he thinks that after development of the organ is completed similar structures, secondary islands of Langerhans, are formed from groups of secreting acini.

Various opinions are held concerning the nature of the interacinar cell groups. The suggestions which have been advanced may be classified as follows: (1) The islands of Langerhans, having the same origin as the secreting elements of the gland, are formed during embryological life and persisting thereafter probably subserve some special function. (2) They represent a stage in the embryological development of the gland acini and those found in the adult organ are persistent rudimentary structures. (3) They are follicles of lymphatic tissue scattered through the organ. (4) They are modified acini, transformed as the result of functional activity of a peculiar nature.

When throughout the gland structures are found composed of cells differing from those of the acini, having a different arrangement and bearing a peculiar relation to the blood-vessels, it seems probable that, formed in embryological life, they possess an anatomical identity as definite as that of the glomeruli of the kidneys or the Malpighian bodies of the

[1] Langerhans. Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse. Inaug.-Diss., Berlin, 1869.

[2] Renaut. Sur les organes lymphoglandulaires et la pancreas des vertebres. Compt. rend. d. l'Acad. d. Sciénces, LXXXIX, 247, 1879.

[3] Podwyssotski. Beiträge zur Kenntniss des feineren Baues der Bauchspeicheldrüse. Arch. f. mikrosk. Anat., XXI, 765, 1882.

[4] Kühne and Lea. Beobachtungen über die Absonderung des Pancreas. Untersuch. a. d. Physiolog. Instit d. Univ. Heidelberg, II, 488, 1882.

[5] Harris and Gow. Note upon One or Two Points in the Comparative Histology of the Pancreas. Jour. of Phys., XV, 349, 1894.

[6] Diamare. Studii comparativi sulle isole di Langerhans del pancreas. Internat. Monatsschr. f. Anat. u. Phys., XVI, 155, 177, 1899.

[7] Laguesse. Sur les principaux stades du développment histogenique du pancréas. Verhandlungen der anat. Gesellsch., 1897, 43.

spleen. Schäfer[8] thinks that they are similar to the small ductless structures, the carotid and coccygeal glands and the parathyroid bodies which are like them composed of anastomosing columns of epithelial-like cells, between which is a network of delicate tortuous capillaries.

Laguesse[9] has suggested that these structures represent a stage in the development of the glandular acini but has subsequently abandoned this view, in support of which there is no evidence. A number of observers have emphasized the supposed resemblance of the interacinar islets to lymphoid tissue. Renaut[10] has described the pancreas as a lympho-glandular organ composed, he conceives, of glandular structures and lymphoid tissue in intimate relation. He describes the cell groups as "points folliculaires," in which cells of a glandular type are situated in the meshes a reticular tissue. Mouret[11] has supported Renaut's somewhat ill-defined conception of a lympho-glandular organ, but has regarded the cell group as small masses of lymphoid tissue. Kühne and Lea and Dieckhoff[12] think it probable that they are small lymph follicles. Schlesinger[13] regards them as a variety of lymph follicle whose cells differ from those of ordinary lymphoid tissue. Podwyssotski calls them pseudo-follicles and states that though they resemble lymph follicles their cells have nothing in common with lymphoid cells.

The only attempt to investigate experimentally the nature of the islands of Langerhans has been made by Lewaschew,[14] working in Heidenhain's laboratory. He studied the pancreas of dogs and cats, killed after having been subjected to conditions which cause the gland to secrete actively. After prolonged overfeeding or after the administration of pilocarpin, which stimulates the pancreas as it does the salivary glands, he claims to have found structures representing transitions between the gland acini and the interacinar cell group. He observes acini containing one or more cells whose protoplasm is non-granular and stains lightly. A whole acinus or a number of acini may be composed of such cells. In such areas some of the cells may assume a polygonal shape and are no longer grouped to form a central lumen. Other cell groups consist entirely of polygonal cells without acinar arrangement, and these represent, he thinks, the fully formed islands of Langerhans.

In order to obtain a large increase in the number of altered acini one even maximal stimulation of the gland is not sufficient, but by the repeated administration of pilocarpin this result is accomplished and the longer and more intense the action of the drug the greater their number. To cause their increase by overfeeding a very large quantity of food is necessary. Lewaschew believes that the cells composing the interacinar groups may reassume the characters of secreting cells and again form acini. He mentions that he has found an unusual number of islands under conditions other than those of increased functional activity. They were very numerous in a dog which several days before its death had suffered with fever.

The observations of Lewaschew have not been confirmed. In the human pancreas one occasionally finds altered glandular cells. Non-granular refractive cells may occur in otherwise normal acini and entire acini or groups of acini may be composed of such cells. Laguesse,[15] regarding them as transitions between acini and interacinar groups, has adopted the view of Lewaschew.

It is by no means surprising that little is known concerning the function of structures whose nature is so little understood. Laguesse[16] thinks that they represent secreting acini temporarily modified to adapt themselves to a new function, the elaboration of an internal secretion. Schäfer[17] and Diamare think that the vascular islets probably furnish an internal secretion. The only evidence in support of this suggestion is contained in the short preliminary notice of Ssobolew.[18] He states that after feeding animals on carbohydrates the cells of the islands become more granular. After ligating the duct of Wirsung in dogs the islands of Langerhans, he finds, are not involved in the sclerotic process which follows. He thinks that this fact explains the absence of glycosuria after ligation of the pancreatic ducts. In human cases I had observed after duct obstruction[19] similar resistance of the islands to the consequent inflammation. In pancreas of two diabetics Ssobolew was unable to discover islands of Langerhans.

I have attempted to determine the relation of the islands of Langerhans to the other elements of the pancreas. They have been observed in human cases under a great variety of conditions, in cats and in dogs. Their relation to the blood-vessels has been studied in injected specimens. Finally, I have attempted to repeat the experiments of Lewaschew in order to test the possibility of transforming acini into interacinar cell islets.

In the human pancreas the islands were found to be more numerous in the splenic end or tail than elsewhere. To obtain a numerical statement of their relative abundance, their num-

[8] Schäfer. Quain's Anatomy, Vol. III, Pt. IV, p. 318.

[9] Laguesse. Sur la formation des îlots de Langerhans dans le pancréas. Compt. rend. Soc. de biol., 9. S., V. 819, 1893.

[10] Renaut. Loc. cit.

[11] Mouret. Tissue lymphoide du pancreas et cellule centro-acineuse. Compt. rend. Soc. de biol., 10. S. I., 731, 1894.

[12] Dieckhoff. Beiträge zur pathologischen Anatomie des Pancreas. Festschrift f. Thierfelder, Leipzig, 1895.

[13] Schlesinger. Die Erkrankung des Pancreas bei hereditärer Lues. Virch. Arch., CLIV, 501, 1898.

[14] Lewaschew. Ueber eine eigenthümliche Veränderung der Pankreaszellen warmblütiger Thiere bei starker Absonderungsthätigkeit der Drüse. Arch. f. mikros. Anat., XXIV, 452, 1886.

[15] Laguesse. Sur quelques détails de structure du pancreas humain. Compt. rend. Soc. de biol. S. 10., I, 667, 1894.

[16] Laguesse. Compt. rend. Soc. de biol., 9. S., V, 819, 1893.

[17] Schäfer. Internal Secretions. Lancet, 1895, II, 321.

[18] Ssobolew. Ueber die Structure der Bauchspeicheldrüse unter gewissen pathologischen Bedingungen. Centralbl. f. allg. Path. u. path. Anat., XI, 202, 1900.

[19] Opie. Pathological Changes Affecting the Islands of Langerhans of the Pancreas. Jour. Boston Soc. Med. Sciences, IV, 251, 1900.

ber was determined in a sectional area of 0.5 square centimetre. Sections about 10 μ thick were made from the enlarged duodenal portion of the pancreas or the head, from the mid-portion or body and from the splenic end or tail. The following table gives their number in an area of 0.5 square centimetre in sections taken from the head, body and tail of ten normal organs:

TABLE I.

	Head.	Body.	Tail.
I	11	13	30
II	30	25	42
III	4	4	19
IV	4	10	13
V	27	18	59
VI	25	27	26
VII	18	18	29
VIII	6	10	29
IX	44	32	61
X	14	23	32
Average	18.3	18.0	34.0

The table shows that the islands are more abundant in the tail or splenic end than in the head and in the body, where they are present in approximately equal number. They are almost twice as numerous in sections from the tail as in those from other parts. Since the number in only one plane is recorded, in order to obtain their actual relative abundance it is necessary to square these figures. They are then found to be slightly less than three and a half times as numerous in the tail as elsewhere.

The islands of Langerhans are more numerous, as pointed out by Kasahara,[20] in the pancreatic tissue of the fœtus and of very young children than in that of the adult. Should we assume that they are formed during embryological development and persist thereafter, this fact is readily explicable. The organ being much smaller in the fœtus and in the young child, the same number of islands, though themselves smaller, are closer together and therefore appear to be more numerous in sections.

The cells composing the islands resemble those of the acini. They have a large round, occasionally oval, vesicular nucleus and a conspicuous cell body. The basal zone of the secreting cell, as is well known, stains deeply with nuclear dyes, for example, hæmatoxylin or methylene-blue, while the central portion which contains zymogen granules remains unstained. The cells of the island, however, do not stain with nuclear dyes, while with eosin their protoplasm takes a homogeneous bright pink color. The nuclei differ but little from those of neighboring acini. They vary considerably in size and not infrequently one finds very large round vesicular nuclei whose diameter is two or more times that of those about. Occasionally the cells, forming columns between which are the anastomosing capillaries, are very closely packed together and nuclei are situated almost side by side; more frequently the cells of the island are less numerous and the nuclei are less closely crowded together.

The outline of the island is usually round or oval and is not infrequently accentuated by a delicate circle of fibrous tissue. In other instances the outline is less sharp and the body accommodates its shape to that of the neighboring acini. Occasionally one sees, apparently within the island, cells arranged, as in the acini, about a central lumen and, indeed, in many instances it is difficult to convince one's self that they do not form part of it. The impression is produced that the columns of the island are in continuity with cells having an acinar arrangement. Since the islands and the secreting acini have a common origin it is not inconceivable that they may occasionally remain continuous in the adult organ. When the fœtal pancreas is affected by congenital syphilis, the islands, I have found,[21] retain their continuity with the secreting structures.

In the human pancreas the groups of acini about terminal ducts are not sharply defined by connective tissue, so that individual lobules, as in the human liver, are indistinctly marked off and in places apparently fuse with one another. In the pancreas of the cat the lobules, like those in the liver of the pig, are much more sharply outlined by interstitial tissue. Details of structure have been studied in the pancreas of the cat.

The parenchyma is divided by septa of fibrous tissue into small polygonal areas varying in size and shape. When injected with Berlin-blue a small ramification of the ducts is found to penetrate the isolated group of acini. These subdivisions or lobules often appear completely isolated by fibrous tissue from those nearby, but when one of them is traced through a series of sections its separation may not be uniform and in places one finds the parenchyma of adjacent lobules in contact, the dividing septa being incomplete. That these polygonal structures are actually independent of one another and represent units of structure is readily demonstrated by causing an inflammatory increase of the interstitial tissue. If the pancreatic ducts of a cat are ligated and the animal killed at the end of two or three weeks, the gland is found to be the seat of a chronic interstitial inflammation, characterized by an increase of the interlobular tissue. The lobules are completely separated from one another by narrow bands of firm fibrous tissue and occur in sections as rounded triangular or polygonal areas of parenchyma.

The islands of Langerhans occupy a position near the centre of the lobule and in the splenic end of the gland each lobule contains an island. In a given section many lobules whose limits are more or less distinctly outlined are seen to contain islands situated near their centre, while in neighboring lobules such structures may not be discoverable. If, however, serial sections are studied every lobule is found to contain an island. Its presence within the lobule is not constant in other parts of the organ, and in the extremity

[20] Kasahara. Ueber das Bindegewebe des Pankreas bei verschiedenen Krankheiten. Virch. Arch., CXLIII, 111, 1896.

[21] Opie. Loc. cit.

of the descending arm of the gland they are very few in number.

The lobules are grouped about the medium sized ducts. The main ducts give off branches approximately at right angles to their course. Branching one or more times a duct forms the centre of a group of lobules, which is usually elongated in form and tapers to a point at or near the surface of the gland. Such lobule groups are separated from one another by relatively wide bands of areolar tissue much looser in texture than that separating the individual lobules. The lobule groups in the fresh state or in tissue macerated a few

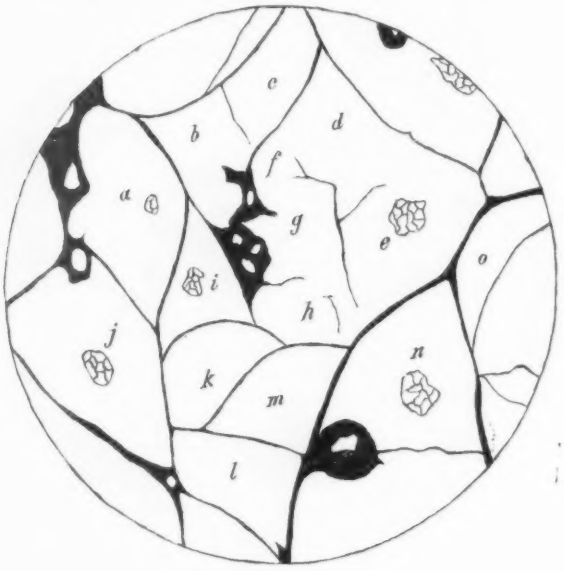


FIGURE 1.—Camera lucida tracing of the lobule boundaries in one of a series of sections from the splenic end of a cat's pancreas. The majority of the lobules are well defined. Those marked *d*, *e*, *f*, *g* and *h* are poorly outlined but are found to be more readily distinguishable when traced through the series of sections. The lobules, which are lettered (*a* to *o*), were traced through the series and each was found to contain an island of Langerhans situated near its centre. The section passes through the island in lobules *a*, *e*, *i*, *j* and *n*.

days in Müller's fluid may be separated from one another by careful teasing. In the loose tissue lie the larger ducts, arteries, veins, and nerves. An artery and vein penetrate each lobule group in company with the duct and ramify between its lobules. The smallest arteries occasionally penetrate the lobules, but usually branches, diminishing in size, give off capillaries which enter the lobule and form a close network between the gland acini.

The capillaries of the island of Langerhans form a glomerulus of tortuous freely anastomosing vessels, much thicker than those between the acini. A single afferent vessel like that of the glomerulus of the kidney does not enter this group of dilated capillaries but numerous anastomoses make it continuous with the interacinar capillaries. When Berlin-blue is injected through the aorta into the arteries of the pancreas, it not infrequently happens that in portions of the gland which are poorly injected the vessels of the island are filled with the injected mass, while the surrounding capillaries are for the most part empty. If instead of soluble Berlin-blue a granular injection mass, for example, cinnabar or ultramarine blue is used, the islands may be injected while the interacinar capillaries contain little of the injected material. The glomerular network is in very free communication with the smallest arteries and apparently has a richer blood supply than other parts of the lobule.

In the human pancreas lobules and lobule groups are not so regularly arranged as in the cat. But both structures are more or less clearly definable. The lobules vary much in size and are usually not clearly separated from one another. Though an island of Langerhans is often situated in the centre of a more or less clearly defined lobule, no constancy of position is discoverable. The lobule groups are separated by relatively wide bands of loose areolar tissue in which are contained the medium sized ducts, the blood-vessels and the nerves. Within the lobule group the arteries and veins which are side by side do not, as in the cat, accompany the ducts.

In the normal human pancreas one occasionally finds small groups of acini composed of cells differing from the typical glandular type and suggesting a transition from the secreting cell to that of the island of Langerhans. The cell-protoplasm does not take the nuclear dye as does the basal portion of the ordinary glandular cell, and when stained with eosin has a bright pink color and homogeneous refractive appearance. The nucleus, which shows no evidence of degenerative change, is situated near the centre of the cell. Occasionally one or more cells of the character described form part of an acinus which otherwise resembles those about it. Usually, however, a group of acini are changed, and such an area often corresponds in size to an island of Langerhans.

The presence of altered acini whose cells resemble those of the island confirms at first sight the view of Lewaschew that groups of acini may assume the characters of the interacinar structures. It is probable that such foci in part at least represent what Laguesse[22] and Pischinger[23] have described as stages of transition. The arrangement of more or less columnar cells about a central lumen is, however, still preserved and one does not find similar areas in which this arrangement is lost. The lumen, indeed, is usually very conspicuous and is often considerably dilated, filled with products of secretion which stain deeply with eosin. It seems probable that these groups of acini are altered as the result of peculiar functional activity, it may be, of hyperstimulation of the gland. There is at least no evidence that they represent

[22] Laguesse. Compt. rend., S. 10, I, 667, 1894.

[23] Pischinger. Beiträge zur Kenntniss des Pankreas. Inaug.-Diss., München, 1895.

transitional stages between gland acini and islands of Langerhans.

Such altered acini are observed in a small proportion of normal glands. They were found in three of twenty-seven glands examined carefully for their presence. They were present in three of seven relatively normal organs from diabetic patients. The occurrence of voracious appetite and increased food ingestion in individuals so affected may explain the occurrence of these areas which represent possibly foci of peculiar secretory activity. They were particularly abundant in one instance of chronic interstitial pancreatitis not associated with diabetes.

Lewaschew has claimed that he was able to transform groups of secreting acini into islands of Langerhans by stimulating the pancreas with pilocarpin. A single administration of the drug does not suffice, but by its repeated administration an undoubted increase in the number of islands may, he says, be obtained. Under such conditions these bodies appeared to be more numerous than usual, but he has made no attempt to determine their actual number. He does not record the amount of pilocarpin used nor the frequency of its administration. His experiments have not been repeated.

I have attempted to confirm the observations of Lewaschew by injecting subcutaneously pilocarpin muriate into dogs. Since the number of islands was found to vary in different parts of the gland, it was considered desirable to study sections from corresponding parts of the organ. Specimens were prepared from (a) the splenic extremity, from (b) the portion which is in contact with the duodenum, and from (c) the descending portion which lies in the mesentery of the duodenum. In order to determine with accuracy the relative abundance of the islands their number was counted in a measured sectional area and compared with that found in the pancreas of an animal to which pilocarpin had not been given.

Following is a summary of the experiments performed:

Dog No. 1.—The animal was given daily for nine successive days 0.02 to 0.03 grm. of pilocarpin muriate. Profuse salivation was produced often with vomiting and diarrhœa.

Dog No. 2.—During twenty-eight hours pilocarpin muriate 0.005 to 0.01 grm. was injected subcutaneously six times. The drug produced profuse flow of saliva.

Dog No. 3.—During twenty-four hours pilocarpin muriate 0.01 grm. was injected subcutaneously seven times. Profuse salivation followed each injection.

In the table the figures represent the number of islands in 0.5 square centimetre of sectional area. The letters refer to the parts of the gland indicated above.

TABLE II.

Injected animal.	a.	b.	c.	Control animal.	a.	b.	c.
Dog No. 1...	61	21	1	Dog No. I ...	59	61	14
No. 2...	55	20	11	No. II...	39	53	3
No. 3...	54	72	8	No. III..	67	89	12
Average	56.6	37.6	6.6	Average	55.	67.6	9.6

The figures show that no increase of the number of islands was obtained in the three experiments. Transitional stages between glandular acini and interacinar islets were not observed. The number of islands in that part of the descending portion of the pancreas which lies in the mesentery of the duodenum (c) is constantly much less than elsewhere. The number in different glands and in different parts of the same gland varies considerably. In the experiments of Lewaschew these sources of error have apparently not been given sufficient weight.

CONCLUSIONS.

(1) The islands of Langerhans are composed of cells having the same origin as those of the glandular acini but forming structures which are independent of the secreting apparatus and in intimate relation with the vascular system.

(2) In the splenic end of the cat's pancreas they have a definite position within the lobule, each of which contains one of these structures.

(3) In the human pancreas they are more numerous in the splenic extremity or tail than elsewhere. Similar variation in their number is observed in cats and dogs.

(4) Prolonged stimulation of the gland does not, as claimed by Lewaschew, transform groups of acini into islands of Langerhans.

THE DISTRIBUTION OF CONNECTIVE TISSUE IN NEW GROWTHS.

BY W. C. WHITE, M. B.

(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

I here report the result of the study of the distribution of connective tissues (viz., yellow elastic tissue, white fibrous tissue and reticulum) in seventeen new growths, obtained in the fresh state from the Surgical and Gynæcological Department of the Johns Hopkins Hospital through the kindness of Dr. Cushing and Dr. Kelly.

The work was done in the Pathological Laboratory of the Hospital at the suggestion of Dr. L. F. Barker, and I am much indebted to him for his willing and valued assistance throughout. To Dr. F. P. Mall I am also under obligations for many kind suggestions.

The following methods were employed:

1. For the study of elastic tissue.

(*a*) Demidessication and artificial œdema; fresh tissue stained with magenta.

(*b*) Weigert's[1] elastic fibre staining of the hardened tissue.

(*c*) Unna's orcein stain (hardened tissue).

2. For the study of white fibrous tissue and reticulum.

(*a*) Mall's method.[2] Digesting the fresh frozen section in pancreatin solution.

(*b*) Spalteholtz' method.[3] Digesting sections of hardened tissues in pancreatin solution, alternate sections being stained with hæmatoxylin and eosin for comparison.

(*c*) Van Gieson's picric acid fuchsin stain.

(*d*) Mallory's new connective tissue stain, the use of which was very kindly permitted by Dr. Mallory, although the formula is still unpublished.

In studying the distribution of these tissues it has been taken for granted (1) that the tissue staining purplish with magenta in the fresh preparations and deep blue with Weigert's stain in the hardened preparation is elastic tissue, and (2) that the tissue left after digestion in pancreatin solution and staining red with Van Gieson's stain and blue with Mallory's stain is either white fibrous tissue or reticulum, and I have called them such in writing this paper.

The object has been, not to study the distribution of one kind of connective tissue, but to study the character and distribution of the several kinds by many methods.

It has been a great drawback that there is as yet no certain method of distinguishing white fibrous tissue and reticulum. Siegfried[4] has found in reticulum a substance which he calls reticulin, thus distinguishing it from white fibrous tissue which yields gelatine, but this method was not practically applicable in the present study. Then certain structural differences, it is asserted, exist between the two substances; viz., the wavy more or less parallel fibrils of white fibrous tissue running in bundles as against the very fine anastomosing and branching fibrils of reticulum; but the two substances are so intimately associated in any structure that the question arises of the possibility of the one being the final breaking up and division of the other.

In the sarcomata and myomata reticular networks were found which in structure coincided with reticulum, the fibrils definitely branching and anastomosing, but they were here intimately associated with bundles of wavy parallel fibres which were just as typical of white fibrous tissue. In some places this reticular network appeared to have its origin from these bundles, while in other cases it seemed only to gain an anchorage there, the fibrils extending only for a short distance among the fibres of the bundles. In other places, and this was very frequent in the sarcoma sections studied by Mall's method, the fibrils of the reticular network appeared to arise from certain focal points suggesting the possibility of their being the processes of cells which had been digested away, but the most probable explanation of this appearance was to be found in the thickness of the sections, several fibrils overlying one another at certain points. Again, the fibrils which presented the structural characters of white fibrous tissue were frequently seen in the Mall preparations to break up into much finer fibrils, suggesting the possibility of the two substances, white fibrous tissue and reticulum, being the same substance, the latter being the final division of the former.

So that without some method of determining the distinction or relation between the two substances the description of what was found in the present study has necessarily been purely objective, the two substances being included under the one head. Still some endeavor was made to discover the relation after pancreatin digestion of what was found in myomata to tendon and also to reticulum by the following methods suggested by Dr. Mall.

Tendon was obtained from the human tendo-achillis. Reticulum was obtained from the gut of a dog by drawing the small intestine between the handles of a pair of scissors and thus removing the muscular coats and mucous membrane, leaving only the submucosa. A myoma was secured after removal from the human uterus. Small sections of all three were cut and digested in pancreatin solution.[5]

They were then thoroughly washed in water and later placed in test tubes containing (1) ½ per cent hydrochloric acid; (2) 1 per cent hydrochloric acid; (3) 1 per cent solution of caustic potash and immersed in a beaker of boiling water and the results tabulated.

I have given also by permission the tables of Dr. Mall[6] and of Dr. Flint.[7]

TABLES.

Dr. Mall's Table.

	Time taken to dissolve tendon.	Time taken to dissolve reticulum.
Boiling KOH 1%	30 seconds.	1.5 minutes.
Boiling HCl ½%	1 minute.	18 minutes.

Tissues remaining in the solution one hour before boiling.

Dr. Flint's Table.

Solution.	Time required to dissolve. Tendon.	Adrenal reticulum.	Lymph gland reticulum.
HCl 0.5%	3¼ mins.	10 mins.	11½ mins.
KOH 0.13%	3 mins.	14¾ mins.	22 mins.

In Dr. Flint's work the sections remained in the solutions two hours before boiling, and at the end of the time given the tendon was completely dissolved and the solutions clear, while the reticulum in each case remained as a granular detritus even after boiling for thirty-five minutes.

Solution.	Time required to dissolve Tendon.	Reticulum.	Myoma.
Boiling HCl .5%	27 mins.	43 mins.	55 mins.
" HCl 1%	12 mins.	22 mins.	27 mins.
" KOH 1%. ...	27 mins.	29 mins.	30 mins.

At the end of the different times given the tendon in each

[1] Centralbl. f. alg. Path. u. path. Anat. IX, 1899.

[2] Johns Hopkins Hospital Reports, Vol. I, 1896.

[3] Archiv f. Anat. u. Phys., Anat. Abth., 1897, Supp. Bd.

[4] Habilitationsschrift, Leipzig, 1892.

[5] Pancreatin (P. D. & Co.), 5 grm.; sodium bicarbonate, 10 grm.; water, 100 cc.

[6] Loc. cit.

[7] The Blood Vessels of the Adrenal. Contributions to the Science of Medicine. Dedicated to Wm. H. Welch, Baltimore, 1900.

case was completely dissolved and the fluid remained quite clear, but in the case of both the reticulum and the myoma there remained a minute granular detritus in a very cloudy or turbid fluid. The appearance of tendon was also quite different both from the myoma and the reticulum, which two latter substances behaved very similarly. The edges of the tendon section within a few minutes became very much swollen and assumed a gelatinous or translucent appearance, and this gelatinous area increased at the expense of an opaque centre, but at the same time dissolved away until all had passed into solution. The myoma and reticulum, on the other hand, became shreddy and granular in appearance and gradually broke up into very minute granules which remained suspended in the fluid. In the myoma in the 1 per cent hydrochloric acid solution it was noticed at the end of four minutes that there appeared some swelling and translucency at spots on the surface, but this had all disappeared at the end of ten minutes and after this it behaved very similarly to reticulum. A longer time was taken to accomplish the solution than in the other two tables, but this was probably due to the larger sections used. In the latter cases frozen sections were used, while in this work the pieces measured probably .5 cm. square. In the caustic potash experiment the section of tendon was somewhat larger than the other two sections.

Also based upon Mall's[8] finding that tendon is much more quickly dissolved in pepsin solution than either reticulum or yellow elastic tissue, several frozen sections of myoma were digested for twenty-four hours in pancreatin solution, then washed in water and subsequently put in pepsin solution in the thermostat and removed at different times, 5, 10, 15 and 30 minutes. Mall found that tendon was completely dissolved in a strong solution of P. D. & Co.'s pepsin in from 5 to 30 minutes, while elastic tissue and reticulum only begin to be dissolved at the end of this time. In these sections all evidence of structure was lost, even at the end of five minutes, but at the end of thirty minutes a considerable portion, possibly amounting to one-third of the original section was removed upon the slide. This experiment, however, loses much in value from the fact that no control specimens of either tendon or reticulum were made.

Regarding the two methods of studying white fibrous tissue and reticulum by digestion, viz., that of Mall and that of Spalteholtz, each one gives evidence of value that is not obtained from the other, and as Flint says, both should be used together since in Mall's method owing to the thickness of the section a suggestion of a third dimension is obtained and the fibrils may be traced in most cases throughout their entire course. On the other hand, of the relation of the connective tissue to the cells of the growth very little can be studied owing both to the spreading of the section in mounting and to the difficulty in obtaining a near control section.

In Spalteholtz' method, however, since alternate sections are easily obtained, one being digested and the other stained intact, the relation of cells and connective tissue is readily studied, but owing to the thinness of the section the fibrils are cut short and in many cases appear only as minute spirillar forms, it not being possible to follow their course for any distance.

The subject of elastic tissue in new growths has received a number of contributions since the publication of Weigert's elastic fibre stain.

Melnikow Raswedenkow in Ziegler's Beiträge, Bd. 26, 1899, has described the distribution of elastic tissue in various organs in normal and pathological conditions, and states that elastic fibres in healthy and diseased tissues are derived mainly from the vascular walls, and further that in tumors no new formation of elastic tissue occurs. In the discussion on the paper, however, in the German Pathological Society in Munich,[9] a number of observers reported cases where an increase in amount was present. Hansemann reported a large increase of elastin in a case of metastatic tumor in the spleen but had not found any, as a rule, in malignant growths. Schmorl reported a case where numerous elastic fibres were found in a carcinoma of the stomach. Orth and Nauberck found in carcinomata cases very many elastic fibres present.

Alice Hamilton[10] has reported a case of fibro-sarcoma of the brain in which there was a very large amount of elastic tissue present; the tumor presented a very peculiar rosette arrangement and in places masses of considerable size surrounding blood-vessels, all of which masses were of a fibrillar nature, but elastic tissue was also present as wavy fibrils running among the cells without any apparent relation to a vessel wall or to the cells of the growth. She agrees with Melnikow Raswedenkow as to the origin of elastic fibres from vessel walls but contradicts his statement that in tumors no new formation of elastic tissue occurs. In this case the amount was much more than normal, but the relation was frequently to the periphery of the vessel wall, and where this relation was not found, the presence of elastic tissue was ascribed to the obliteration of the vessel or to the severance of the original connection of the fibres.

H. W. Williams,[11] in a paper on the new formation of elastic fibres, gives a report of his study of 37 cases of carcinoma; 12 in the liver, 4 in lymph nodes, 2 in the thoracic duct, 2 in large veins, 2 in the cerebrum, 1 in the lung, 8 in the mammæ, 1 in the skin, 1 in the stomach and 1 in the rectum. The following are his conclusions:

1. When the stroma of a carcinoma is itself of new formation it is usually free from elastic fibres.

2. Newly formed elastic fibres may occur in the stroma, though rarely, and they are likely to be fine in quality and small in number.

3. The tumors in which newly-formed elastic fibres occurred either contained a large amount of connective-tissue

[8] Johns Hopkins Hospital Reports, Vol. I, 1896. Reticulated Tissue.

[9] Centralbl. f. alg. Path. u. path. Anat., X, 832.

[10] Jour. of Exp. Med., Vol. IV, Nos. 5 and 6, 1899.

[11] Contributions to the Science of Medicine. Dedicated to Wm. H. Welch. Baltimore, 1900.

stroma or the newly-formed fibres were in connection with pre-existing elastic elements of the original parts.

He found evidence of new formation in three cases of carcinoma of the liver. In carcinomata of lymph nodes the stroma was usually free from elastic tissue and when present it was not possible to demonstrate its new formation. In one carcinoma of the thoracic duct there was new formation and in two of the venous growths. In two of the cerebral cases, one secondary from an adeno-carcinoma of the lung and one secondary from the stomach, there were fine elastic fibres present possibly connected with some prolongation of the pia mater. In the carcinomata of the mamma nothing was seen to prove new formation.

Kromayer[12] found in rapidly-growing condylomata, warts and carcinomata of the skin no newly-formed elastic fibres. These were present, however, in older papillomata and fibromata.

There are also a considerable number of papers on the new formation of elastic tissue in other pathological conditions, to which reference will be found in Dr. Williams' paper.[13]

In seven of the seventeen cases in the series here reported elastic fibres were found, the description of which will be found under the individual cases. In all cases they apparently had their origin from the vessel walls. In only one case, No. 6, a carcinoma of the breast does there seem to be sufficient ground for claiming an increase in amount or a new formation. The sections from this case were compared with those from three normal breasts and three other carcinomata and contained a much greater amount of elastic tissue than any of the others.

The safest method of judging the amount of new formation if such exists in any case would seem to be that of comparison of sections of the growth with sections of the normal tissue in which the growth was situated. This, unfortunately, was only done in one case (case 18). In this case a portion of the normal breast in which the carcinoma had grown was prepared in the same way as the growth itself. A description of the comparison will be found under this case.

Regarding the origin and normal development of elastic fibres whether from the transformation of cells, by fusion, into fibres or from the transformation of the intercellular matrix there is still no satisfactory answer.

On the subject of the study of tumors by digestion methods no literature was to be found.

Description of Individual Cases.

Specimens Nos. 1, 4 and 8. Fibromyomata of the uterus.

Elastic Tissue.—In these cases there were no elastic fibres found either in the fresh preparations or in the hardened sections stained with Weigert's elastic fibre stain.

White Fibrous Tissue and Reticulum.—To the naked eye these sections gave the appearance of a fibrillary structure and under the dissecting microscope the fibrillary nature was more clearly seen. The tissue remaining after digestion was collected in places in thick masses and strands, from both of which branches were given off and these again branched in turn. The thicker strands presented in places a distinct whorled appearance, and between the masses and strands minute wavy fibrils were seen running in a more or less parallel direction and passing into and becoming continuous at either end with the thicker portions of the section.

Under the low power of the microscope the masses formed nodal points from which prolongations were given off, an infinite number of very fine fibrils appearing in places.

The larger strands were composed of minute fibres in very close apposition to one another. These strands divided and united again and gave off branches, and from these branches

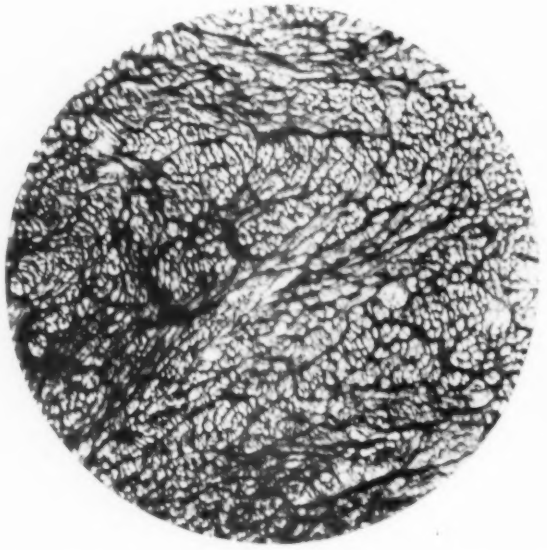


Fig. 1.—Section of a fibromyoma digested by Spalteholz' method, showing the bundles of white fibrous tissue and the reticular network in the meshes of which the muscle cells lay.

and from the sides of the strands themselves there arose exceedingly minute, very wavy, interlacing fibrils running in a course more or less parallel to one another, and in some places arising from one strand and passing into and becoming lost in another strand.

In other parts of the section between the strands was seen a very fine network similar to that obtained by Spalteholtz' method to be described later.

With the high power the fibrillary nature was more clearly seen in some parts, the fibrils being very wavy, in others quite straight throughout their course. The strands themselves were composed of the wavy interlacing fibres of white fibrous tissue while the minute network presented very much the ap-

[12] Monatsschrift f. prakt. Dermatologie, Bd. XIX.

[13] Loc. cit.

pearance of reticulum except that in these sections no definite anastomosis was observed.

In the preparations by Spalteholtz' method very little could be made out either with the naked eye or with the dissecting microscope, but with the latter very minute apertures throughout the section were plainly seen.

Under the low power, however, the condition described under the Van Gieson and Mallory preparations is very clearly seen; viz., a connective-tissue envelope for each muscle-cell.

The connective tissue was very abundant and formed by far the major portion of the section. It was arranged in two ways.

1. Running in every direction and forming a large irregular network, leaving meshes of varying size, were large strands composed of wavy interlacing fibres which followed a more or less parallel course. In places these strands divide and unite again, leaving spaces which are occupied by the network to be described later. In the midst of these strands are seen also the apertures of blood-vessels surrounded by denser tissue, the size of the vessel varying with the size of the strand.

2. In the meshes formed by this stroma was found a minute network apparently formed by the division, subdivision and anastomosis of the branches of this stroma proceeding from all sides of it as it surrounded the individual spaces. The minute meshes of this second network are filled in the control specimen with single muscle cells.

Van Gieson Preparation.—To the naked eye the general impression of this section was red, but on holding it up to the light areas having a yellowish tint were seen. These varied in size and were surrounded by a capsule of deep red. Besides these areas there were certain parts of the section of a lighter and apparently uniform red color, intimately connected with the capsules of the yellowish areas. The capsules surrounding the yellowish areas formed an irregular network throughout the remainder of the section.

With the dissecting microscope the darker capsules mentioned above were seen to run through the section looking like an injected vascular network. The branches from this network ran into and divided the yellowish areas which they surrounded into still smaller areas.

The lighter reddish masses seen with the naked eye were here not so uniform in color, but appeared as a very close network of red stained tissue, and held in the meshes of this network were yellowish cell bodies similar to those found in the other areas, but here the red stained material was much more abundant, the strands being thicker and the meshes smaller.

The general network of red stained connective tissue was irregular, the meshes varying in size, the larger bundles of red surrounding the larger yellowish areas and branches from these forming the walls of smaller areas, but even in the larger strands of red, small groups of yellowish cells were frequently seen.

With the low power the uniform reddish masses were seen to be composed of a dense network of comparatively thick strands of red with small meshes containing the yellowish cell bodies. These yellowish cells were evidently the muscle cells and will be so called in the further description.

The general network of red could be traced with this power to much smaller divisions, in some cases the branching and anastomosing forming so small a network that the meshes of the same contained only a single muscle cell.

The larger strands of red-stained connective tissue had in places a definite whorled appearance and throughout their substance were seen scattered the connective-tissue corpuscles. In these strands were also seen numerous blood-vessels, the larger ones occurring in the larger strands and so on. The muscle cells of the walls of these vessels were stained yellow, similarly to those contained in the general network.

Under the high power the network of connective tissue could be traced to still finer divisions, so that each muscle cell was here seen to have an enveloping capsule of its own, very fine in most instances but comparatively thick in others. In the midst of the larger strands occasional muscle cells were also present.

Mallory's stain gave a very similar picture to that obtained by Van Gieson's stain.

Specimen No. 2 was from a sarcoma of the uterus, but contained so small a portion of sarcomatous tissue that it was of very little service for study; still in the Spalteholtz preparation a reticular network similar to that found in other sarcomata was demonstrated in one portion of the section.

Specimen No. 3 was a portion of the wall of a multilocular ovarian cyst and showed only a dense white fibrous tissue structure in which no elastic fibres were found.

Specimen No. 5 was an epithelioma of the inferior maxilla. This growth was of five and one-half years' duration, but for one year previous to its removal had grown very rapidly. It involved the whole depth of the left half of the inferior maxilla from the ramus behind to a point 2 to 3 cm. beyond the middle line in front. It presented a lobulated appearance with a reddish surface looking like granulation tissue and had an actively growing appearance.

No elastic tissue was found by either method except around the vessels.

Mall's preparation was very unsatisfactory for study; the connective tissue remains forming a more or less solid mass, from which nothing but a fibrillary construction could be made out.

Spalteholtz' method showed a distribution of connective tissue similar to that described below under Mallory's stain, the parts of the control section occupied by the large irregular masses of cells being in the digested specimen quite devoid of connective tissue.

The section stained by Mallory's stain gave in this case the best idea of the distribution of the white fibrous tissue, its absence in the cellular areas and its distribution being controlled by the Spalteholtz' preparation.

The ground work of the section was made up of extensive

strands and bay-like processes of epithelial cells joined together by their minute protoplasmic processes which were very plainly visible and appeared in places as a reticular network; of this, however, nothing remained after digestion. These strands of cells formed a connected network but in certain places became condensed, lying much closer together in rows surrounding larger and smaller irregular spaces which contained a fine loose network of connective tissue, holding in its meshes numbers of connective-tissue corpuscles and polymorphonuclear cells.

The connective tissue in these spaces was collected in the centre into bundles and masses of wavy fibres, and from these minute fibrils radiated outward in all directions as an exceedingly minute fibrillary network, becoming gradually looser in texture until at the edge just inside of the rows of cells they curved and formed an interlacing ring of tissue which, however, sent no processes among the cells of the growth. This latter condition was only demonstrated by the Spalteholtz' preparation.

In several of these spaces there were also seen small blood-vessels swung in the network.

Besides the connective tissue in these spaces there were several strands of white fibrous tissue fibrils which divided the section into smaller portions, but had not been invaded by epithelial cells. These strands were evidently the origin of the connective tissue in the spaces, as many of the latter were found continuous with the former. The connective tissue in the isolated spaces had apparently been shut off by the invasion of the epithelial cells and had then commenced to throw out new fibrils, for in these spaces the connective tissue corpuscles were in a very actively multiplying condition, the nuclei dividing and undergoing mitotic changes.

The larger strands carried in their substance several large blood-vessels. In one or two places in the sections areas of degeneration were present filled with granular debris and polymorphonuclear cells, and around these areas, extending for some distance among the surrounding cells, many polymorphonuclear cells were to be found.

Specimen No. 6 was part of a carcinoma of the left breast in a woman 56 years of age. The growth was of one year's duration and at the time of removal measured 5.5 x 5 cm. Besides this larger nodule there was a second smaller growth 4.5 x 4.7 cm. in size. The nipple was slightly retracted and there were metastases in the cervical and axillary glands.

Elastic Tissue.—The fresh tissue teased out upon a slide and stained with magenta showed a considerable number of purple stained elastic fibres varying in thickness, quite wavy and curled at their free ends.

The frozen section stained with magenta also showed elastic fibres around groups of cells, around the blood-vessels and lymphatic ducts and also throughout the connective-tissue stroma.

In the preparation hardened in Zenker's solution and stained with Weigert's elastic fibre stain, the sections presented, even to the naked eye, many blue-stained areas, representing the elastic tissue. This was distributed throughout the section in two ways: (1) Surrounding certain definite areas and marking these off distinctly from the rest of the section. (2) As minute lines running for short distances through the balance of the section.

Under the low power the areas mentioned above were composed of the cells of the growth grouped together in varying numbers from 5 or 6 up to many hundreds, and immediately outside of these groups was an irregular or serrated encasement of elastic tissue in single and double layers, and outside of this again a layer of connective tissue in which were scattered many minute fibrils of elastic tissue. These were evidently the lactiferous tubules which had been invaded by the growth. Many elastic fibres were also present in the walls of the blood-vessels. There were also a number of very small areas containing only three or four cells which were completely surrounded with elastic tissue and in some places these areas themselves appeared in groups of three and four. Besides the above distribution there were also numbers of fibres of elastic tissue running in the connective tissue strands in double lines as if the remains of a vessel no longer patent. It was with the high power, however, that the very large amount of very fine elastic fibrils running through the sections could be made out following mainly the white fibrous-tissue framework but often seen among the cells of the growth with apparently no other connective tissue accompanying them.

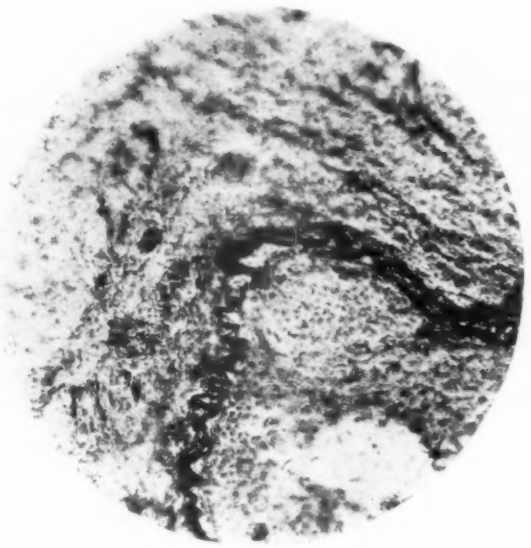


Fig. 2.—Section of carcinoma of breast No. 6, stained by Weigert's elastic fibre stain, showing the distribution of elastic tissue around a large nest of cells and in the surrounding stroma.

Many of the groups of cells were quite devoid of elastic fibrils around them.

There was, apparently, an increase in the amount of elastic tissue in this growth, for in comparison with three normal

breasts two from cases younger than the patient from which the present growth was removed,[1] and three other carcinomata of the mamma, this growth contained a very much larger amount than any of the others. There were also so many minute fibrils differing from that around the vessels and ducts found through the growth away from their apparent origin, that the increase in amount seemed more probable.

White Fibrous Tissue and Reticulum.—Mall's preparation showed a network of strands varying in width from the thickness of writing paper to six or seven times this width, with meshes varying in size from a pinpoint to a pinhead. These meshes were quite clear and appeared as open spaces throughout the section.

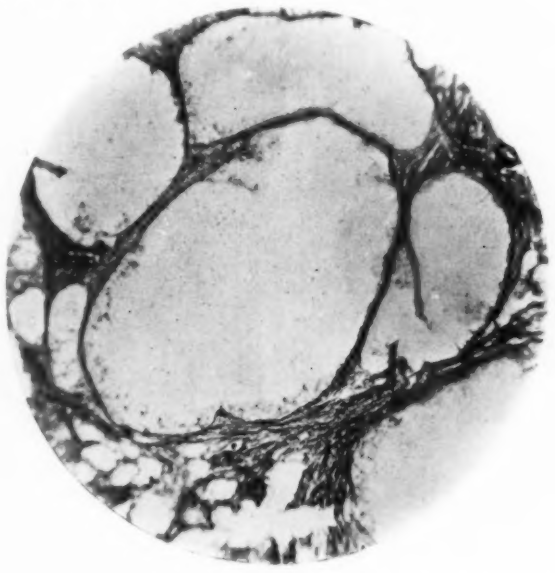


FIG. 3.—Section of a carcinoma of the breast No. 6, digested by Spalteholz' method, showing a group of cell spaces outlined by bundles of wavy fibrils and the entire absence of tissue of any kind in these spaces.

In places the connective tissue forming the network was collected into masses of considerable size up to an eighth or a sixteenth of an inch in size. In other places the larger strands surrounded an open space which was subdivided into two or more smaller meshes by threads of the smallest width. The meshes were for the most part more or less circular in outline.

Sections were examined with low power magnification. The meshes were nearly all quite clear; some, however, had projecting into them from the strands which surrounded them the free ends of the fibrils of which these were composed.

The strands forming the network were composed of minute fibres running in a more or less parallel direction intermingling with one another and for the most part quite wavy, so much so that in places, instead of running a continuous course, certain fibrils appeared as a succession of minute spirillæ. The majority of the fibres could be traced throughout their course.

In many places there was a cross fibrillation, with longitudinal fibrils underlying it, both free ends of the former being seen, evidently the fibrils of the third dimension of the cell space.

In the thinner portions of the section a bundle of fibrils could often be traced down one side of a mesh and curving around a second side, then at the third side dividing some of the fibrils, continuing around the same mesh, while others passed in another direction in the strand between two adjoining meshes and so on, intimately interlacing with one another.

With the high power the finer fibrillary nature of the stroma was much clearer but there was no branching or anastomosis of the fibrils, each being traceable along its course without interruption.

Spalteholtz' preparation showed a number of absolutely clear spaces outlined by wavy fibrils in bundles which in some places completely surrounded them, while in others they were continued onward between two adjoining spaces after passing around one or two sides of a mesh. These clear spaces in the control specimen were filled with the cells of the growth and evidently these had no intercellular substance between them. The rest of the section was occupied by bundles of wavy white fibrous tissue fibrils which frequently separated, leaving clear spaces which were in the control specimen filled with small groups of cells.

Mallory's and Van Gieson's stains threw no additional light upon the distribution of the connective tissue in this growth.

Specimen No. 7 was from a small round and spindle-celled sarcoma removed from the thigh of a woman 59 years of age. The tumor commenced in the adductor muscles of the thigh and extended downward in the muscles to the popliteal space. It did not involve the muscles about the knee joint, but passed between the bones of the leg and involved the muscles on the anterior aspect of this. There were also large glands on the front of the thigh of similar structure. In the thigh it completely surrounded the femoral vessels and extended outward between the muscles four or five centimetres. In the popliteal space it surrounded the popliteal vessels. Portions were obtained from the growth in the thigh through the femoral vessels and from the outside of the growth.

Elastic Tissue.—The fresh specimens, both the teased and the frozen section, stained with magenta showed considerable numbers of elastic fibres varying in size and character from the fine branching fibres similar to those in areolar tissue to the coarser curly fibres resembling those in the ligamentum nuchæ. These fibres ran among the cells of the growth and were found both in the section taken through the femoral vessels and in that from the outside of the growth.

In the Zenker preparation, stained by Weigert's method, the blue-stained elastic fibres were plainly visible to the naked eye. Under the low power the sections were seen to be

[1] The elastic tissue apparently decreases in amount as the mamma atrophies after the menopause.

divided into lobules of different size by strands of white fibrous tissue, the lobules being closely packed with the cells of the growth with very little evidence of intercellular tissue. The elastic fibres occurred in the midst of the strands of white fibrous tissue and were most abundant in the largest strands but also in places running among the cells.

In the strands they existed as very fine straight branching fibres with free curling ends and also as short curly fibres, due possibly to both ends being free. They occurred also here and there in the section as mentioned above as curly fibrils running among the cells.

In the section near the femoral vessels the elastic tissue was much more abundant. With the high power the branching of the elastic fibrils was more apparent. Some of the white fibrous tissue strands were quite free from the blue fibres, and as one proceeded from the femoral vessels outward the amount of elastic tissue grew less, although it was still present in considerable quantity in the sections from the outside of the growth.

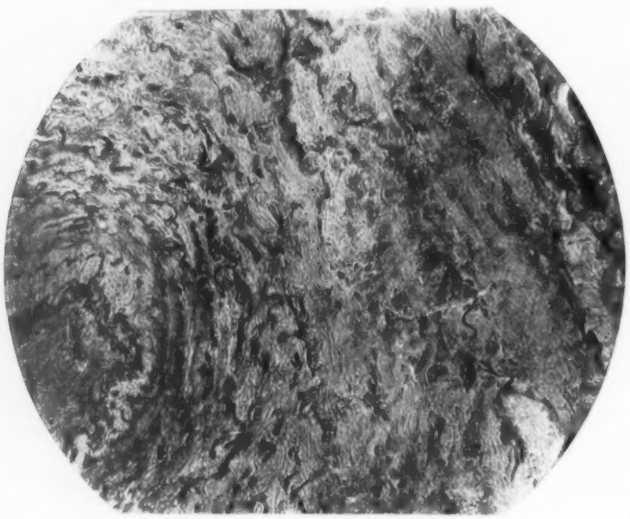


Fig. 4.—Section of sarcoma No. 7, stained by Weigert's method for elastic fibres, showing in dark curling lines the distribution of the elastic fibres. At one side of the section the femoral vessel is seen outlined by elastic tissue and surrounding this are seen layers of elastic fibres lying among the cells of the growth alternating with layers of white fibrous tissue.

A very peculiar arrangement was present around the femoral vessels. The small round cells had encroached upon the walls of the vessel to the endothelial lining, and from this outward were ranged in definite order layers of small round cells with elastic fibres among them, succeeded by layers of white fibrous tissue with very few elastic fibres one above the other for many layers. The fibres near the vessels were, as a rule, much thicker than those found in the outskirts of the growth.

Unna's orcein stain gave a very similar picture to the above with the elastic tissue stained a silky brown.

From the very large amount of elastic tissue found in this growth and from its varying character it would seem fair to conclude that there was considerable new formation of the tissue.

White Fibrous Tissue and Reticulum. Mall's Preparation.—For purposes of description the fibres forming this section after digestion may be divided into two groups:

1. Long wavy, more or less parallel fibres running in bundles through the sections, the fibres interlacing with one another. These were evidently white fibrous tissue, and in the control specimen this tissue divided the section into lobules, and in the Weigert preparation it carried the elastic fibres.

2. Exceedingly fine fibrils which formed the ground work and main portion of the section and lay between the bundles of the first group. They formed a very minute meshwork running in every direction, definitely branching and anastomosing and presenting very much the appearance of reticulum of normal glands. In some places the fibrils appeared to arise from focal points spreading out in all directions and uniting with fibrils from other points.

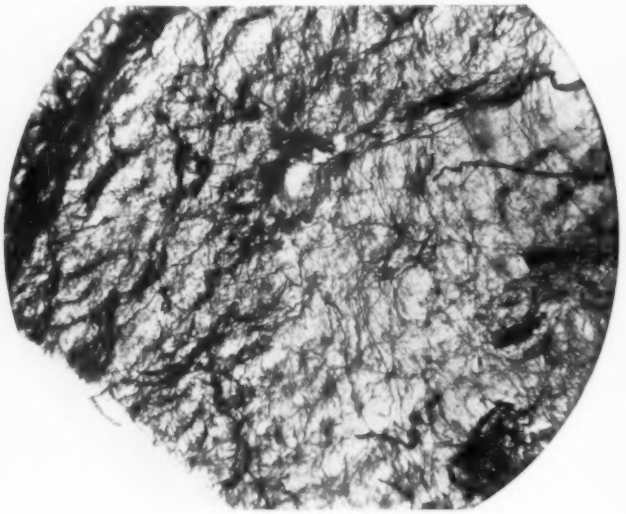


Fig. 5.—Section of sarcoma No. 7, digested by Mall's method, showing the strands of wavy parallel fibrils and the groundwork of minute reticular fibrils occupying the remaining portion of the section. The appearance of a focal origin of these fibrils is quite evident in certain spots.

Under the high power the fibres of the first groups appeared as above but in the reticular network the branching and anastomosing of the fibrils was much more evident. This network seemed to have no direct connection with the first group but extended a short distance among its fibres as if to gain anchorage there, for in the centre of these bundles they were not nearly so evident.

Throughout the section the apparent focal origin of these fibrils may be due to four or five of these overlying each other at a certain spot.

Spaltholz' Preparation.—These sections were much thinner

than those by Mall's method, but showed the same points of interest; the strands of white fibrous tissue dividing the section into lobules, and between these strands, and forming the balance of the section, an exceedingly minute network of delicate fibrils which branch and anastomose, the meshes of which were in the control specimen occupied by the round and spindle cells of the growth, by single cells in most cases, but in some cases apparently by groups of two or three or possibly more. However, in those spaces which were occupied by groups of cells there was often seen in this specimen a small jutting branch as if it had been divided in cutting the section. The apparent focal origin of these fibrils was also noticed in these sections.

Specimen No. 9 was from a carcinoma of the uterus.

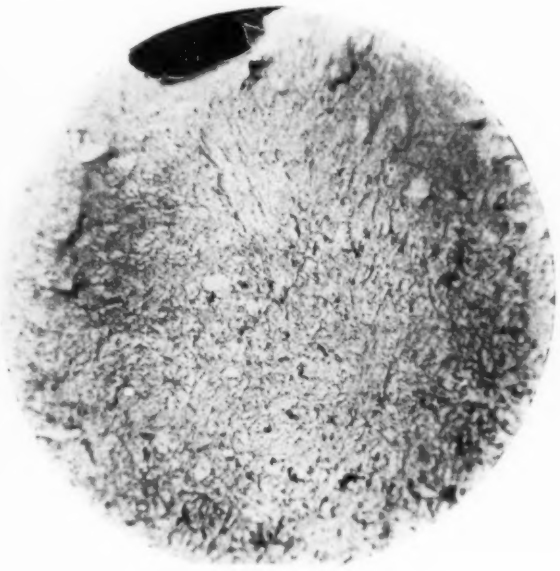


FIG. 6.—Section of sarcoma No. 7 digested by Spalteholtz' method, showing the reticular network with the branching and anastomosis of the fibrils.

It showed no elastic fibres in the fresh preparations but in the hardened section stained by Weigert's stain there were seen in the connective-tissue stroma minute curly fibrils extending for some distance from the vessel's wall, from which they had probably arisen.

White Fibrous Tissue.—The sections studied by Mall's method were too thick for accurate observation but the clear spaces of the carcinomatous growth were clearly seen outlined by bundles of wavy parallel fibres of white fibrous tissue.

In Spalteholtz' preparation the cell nests and groups of cell nests lay embedded in the connective tissue of the muscle wall but were separated from the same by bundles of wavy parallel fibres. These bundles formed a delicate framework, enclosing large meshes which were quite clear in the digested section and filled with cells in the control specimen. Frequently the bundles after passing around one side of a mesh would divide into two smaller bundles which would then take part in the formation of the walls of adjoining meshes. Or again, complete rings of four or five wavy fibres were found in apposition at certain points, leaving between them a clear space, which space was also filled with cells in the control section.

The Van Gieson and Mallory preparations showed the closely packed cell nests lying in the muscle wall of the uterus surrounded by connective tissue, but without the slightest evidence of intercellular tissue.

Specimen No. 10 was from a small round-celled alveolar sarcoma arising from the periosteum of the tibia and invading the tibialis anticus muscle in a girl thirteen years of age. It involved the popliteal glands and also a chain of glands extending along the sciatic nerve.

The growth was exceedingly soft and on cutting it a creamy fluid was expressed.

No elastic tissue was found except around the blood-vessels.

In the preparation by Mall's method the connective tissue was very abundant and disposed in a rather coarse network with comparatively thick strands enclosing varying sized meshes, which to the naked eye appeared quite clear.

Under the low power the section was seen to be composed of a network of thick strands leaving meshes of varying size and shape. The strands were composed of bundles of minute fibres which ran a comparatively straight course. The fibres could often be traced curving around certain meshes, interlacing with fibres going in an opposite direction and continuing on their course around and between neighboring meshes. The meshes were for the most part quite clear. In some, however, there was seen a minute reticular network, the fibrils of which branched and anastomosed.

The meshes in the control specimens were partially filled with small round cells. In many places the meshes were divided by single fibres into smaller meshes, and in some portions of the section where the fibrous tissue was most abundant there was found a definite reticular network outlined by bundles of wavy fibrils. This network was composed of anastomosing and branching fibrils similar to that described in case No. 7. The small meshes of this network were filled with the cells of the growth.

The larger meshes were so loosely filled with cells in the stained specimens that it would seem probable that they had contained also the creamy fluid which was expressed on cutting the fresh tissue.

In Spalteholtz' preparation there was no connected network on account of the thinness of the section. It was composed of minute wavy fibrils running in various directions and outlining irregular spaces which in the control specimen were loosely filled with cells. The white fibrous tissue framework was here of a very loose texture and the interstices left by this separation of its fibres were filled with small round cells in the control section.

In the midst of the clear spaces were frequently seen cir-

cular wavy fibrils completely enclosing small spaces which were also filled with cells in the undigested specimen.

Numerous vessels in the undigested section were represented in the digested section by small rings of connective tissue lying in the framework.

The stained specimens showed numbers of groups of muscle fibres lying among the cells of the growth.

Specimen No. 11 was taken from a carcinoma of the uterus and contained only a very small amount of carcinomatous tissue.

No elastin was present except around the blood-vessels. The other preparations resembled carcinoma No. 9 in every way.

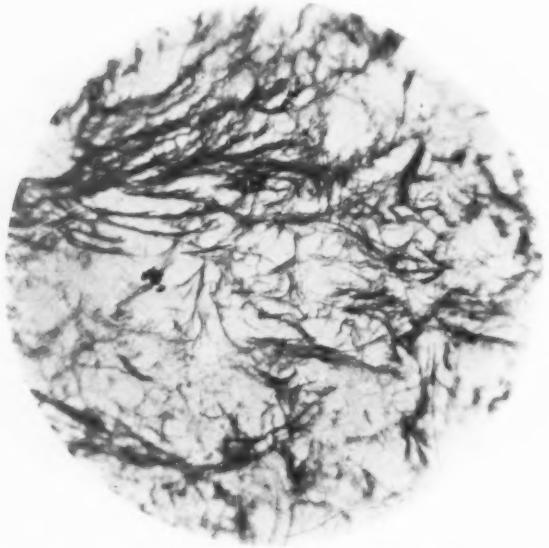


FIG. 7.—Section of scirrhous carcinoma of the breast No. 12, by Mall's method, showing the distribution of white fibrous tissue around the small irregular clear cell spaces.

Specimen No. 12 was a scirrhous carcinoma of the breast from a woman 49 years of age. The growth was of six months' duration and involved also the axillary glands on the same side. The nipple was retracted and the skin adherent to the growth.

This growth showed both in fresh and hardened preparations considerable numbers of elastic fibres around the vessels and lactiferous ducts; also around certain groups of cells, and scattered as short wavy fibrils through the abundant connective-tissue stroma.

In the fresh digested specimen the white fibrous tissue was very abundant in bundles of fine wavy parallel fibres running in every direction and enclosing spaces of varying size. The bundles were in many places very thick and the fibres composing them very close together; these, however, gradually spread out leaving in their midst small clear spaces. Or again, branches from these larger bundles would gradually thin out and divide to enclose clear spaces and frequently these spaces were separated from one another by a single fibril. There was no anastomosis of fibrils and no reticular network. The clear spaces were filled in the control specimen by small groups of cells, the largest containing probably fifteen or twenty cells, the smallest only two or three.

Spaltcholtz' preparation gave in a thinner section much the same picture. Here the wavy fibres were present in bundles which gradually spread out and divided to enclose clear spaces of varying size which were occupied by the cells of the growth in the control section.

This specimen differed from Nos. 6 and 18 (*a*) in the very much larger amount of connective tissue; (*b*) in the smaller and irregular grouping of the cells, and (*c*) in the smaller amount of elastic tissue.

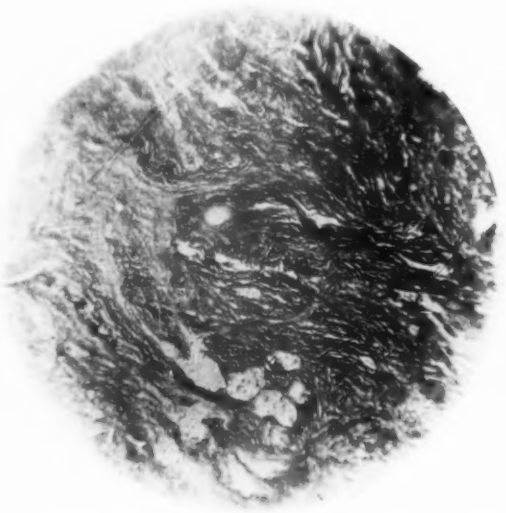


FIG. 8.—Section of fibro-sarcoma of the liver No. 13, by Spaltcholtz' method, showing the large amount of fibrous tissue surrounding the clear cell spaces.

Specimens Nos. 13 and 14 were from carcinomata of the liver and rectum in the same individual. The growth was primary in the rectum, where it formed a mass 7 x 6 cm. in size and filled the whole pelvis. There were numerous secondary nodules in the liver from 2 mm. to 5 cm. in diameter. They were firm, opaque and yellowish and surrounded by a zone of greenish-yellow liver substance. The rectal growth had eroded the sacrum and was adherent to it.

These two specimens were of so similar a nature that only one description will be given for both, noting any differences that existed.

The specimens when obtained had already been kept about four days in the ice chest, so that the fresh preparations for elastic tissue were not satisfactory. In the rectal growth, however, by Weigert's stain a few scattered elastic fibres were found running in the midst of the general white fibrous stroma.

White Fibrous Tissue.—Both growths contained a great deal of connective tissue, the liver growth more than the rectal growth. The type was the same in both, bundles of wavy more or less parallel fibres running in every direction and outlining clear spaces of varying size which were filled with epithelial cells in the control section. These sections resembled very much the scirrhous growths from the breast, but the fibrous tissue was here even more abundant.

In Spalteholtz' preparation the section was thin, the thickness of two or three fibres. The fibres ran in many directions, their further course in any one direction ceasing when they encountered bundles running in an opposite direction. In the midst of the bundles minute openings were seen where the constituent fibrils separated slightly from one another, and in these spaces the connective tissue corpuscles were seen to lie in the control specimen. Here also the curving of the fibres around two or more sides of a clear space and onward between two adjacent spaces was clearly seen.

Specimen No. 16 was from a scirrhous carcinoma of the breast of eight years' growth in a woman forty-four years of age.

This growth resembled very much that described in No. 12. It contained, however, many more elastic fibres running through the white fibrous stroma, but these were confined to the stroma and to the ducts and blood-vessels, and did not in any case surround groups of cells, nor were they nearly so abundant as in case No. 6.

Specimen No. 17 was from a small round and spindle-cell sarcoma taken from the axillary region. It had a thin translucent capsule and could so be separated from the surrounding tissues, the connection consisting only of fine branching connective-tissue fibres and numerous small blood-vessels. Its origin was evidently from the intermuscular connective tissue and the growth itself was soft, elastic and lobulated, measuring 13½ x 10 x 18 cm. Its duration was 20 months, and it involved also a number of glands in the supra-clavicular fossa.

No elastic fibres were found in either the fresh or hardened preparations.

The digested specimens, both by Mall's and Spalteholtz' method, showed the same reticular network as that described in section No. 7, and also the same white fibrous bundles enclosing this network. Neither the Van Gieson nor Mallory preparations showed the large amount present nor its distribution.

Specimen No. 18 was from a carcinoma of the breast of four months' growth in a woman thirty-seven years of age. At removal it was present as a hard regular mass freely movable and measuring 4 x 2 cm. in size.

This was an exceedingly cellular growth, thus differing from cases No. 12 and 16, but it resembled very much case No. 6 both in the distribution of elastic and white fibrous tissue and in the type of cell of which it was composed, except that in the latter instance No. 18 was of a much more malignant type filled with young cells and almost resembling a small round-celled sarcoma.

Elastic Tissue.—The elastic tissue here was disposed in a very similar way to No. 6, but was not so abundant.

In this growth a comparison was made with a portion of normal breast from the same case with reference to the amount and distribution of the elastic tissue with the following result: that the elastic tissue in the growth was found to be not so abundant as in the normal breast, but differed somewhat in distribution. In the normal structure the elastic tissue was confined to the coats of the vessels and lactiferous ducts occasionally occurring in bundles in the stroma of the gland, while in the growth, besides being around the vessels, it was present surrounding large groups of cells, evidently invaded ducts, and as minute wavy fibrils was most abundant in the stroma, but frequently was found in among the cells with apparently no white fibrous tissue accompanying it; also as bundles of fibres which were infiltrated with epithelial cells.

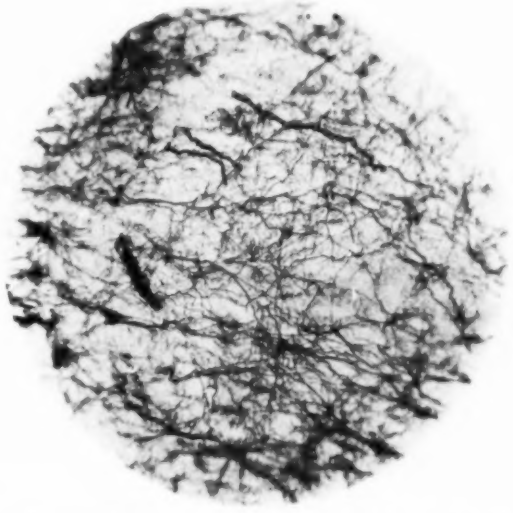


FIG. 9.—Reticular network from sarcoma of axilla No. 18, prepared by Mall's method.

In spite of the very cellular condition of the growth it presented on digestion the distribution of fibrous tissue described under case No. 6 of large cell spaces with no intercellular network.

CONCLUSIONS.

1. Elastic fibres are frequently present in new growths: (*a*) in the stroma; (*b*) among the cells; (*c*) around the blood-vessels, and (*d*) in breast tumors around the lactiferous ducts which have been included and invaded by the growth.

2. When present they are usually in connection with pre-existing elastic-tissue elements in the original tissue in which the tumor has grown.

3. New formation probably occurs but can only be determined by a comparison of that present in the growth with that present in the normal tissue in which the growth has arisen.

4. Sarcomata present a large increase in connective tissue and possess an exceedingly fine intercellular reticular network very similar in structure to the reticulum present in normal glandular tissue.

5. Carcinomata possess a stroma of white fibrous tissue, outlining the cell spaces, but have no intercellular network.

6. The digestion methods present a possible means of diagnosis between carcinomata and sarcomata in doubtful cases.

7. Uterine myomata have a very large amount of connective tissue both of a white fibrous and reticular nature, possessing a connective-tissue capsule for each muscle cell; and it would be more correctly termed fibromyomata.

ON THE RELATION OF THE ELECTRICAL CONDUCTIVITY OF BLOOD-SERUM TO ITS ALLEGED BACTERICIDAL POWER.

By Emma Lootz and Alice Weld Tallant.

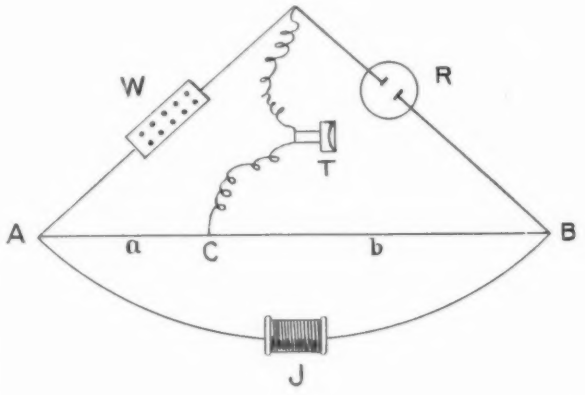
(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

As is well known, it is asserted that blood-serum possesses certain bactericidal properties, and many experiments tend to show that these properties are lost when the serum is heated to from 55-60° C. In a recent article Baumgarten[1] advances the theory that the bactericidal power of the serum is due, not to the actual existence of bactericidal substances in it, but to the fact that bacteria, in being transferred from their natural surroundings to another medium, undergo sudden changes in assimilation and plasmolysis.

Following the line of thought of this article, Dr. L. F. Barker suggested that the writers undertake experiments to discover whether any physico-chemical change could be demonstrated in serum heated to the specified temperature. Electro-chemical examination of the conductivity of the serum was the method chosen, and the following experiments were carried out:

The serum was carefully obtained from dog's blood in the pathological laboratory; the work on conductivity was done in the Chemical Laboratory of the Johns Hopkins University, through the courtesy of Dr. Harry C. Jones. The apparatus used is described by Dr. Jones[2] as follows:

"J is a small induction coil, with only one or two layers of wire. A larger coil must not be used, since it does not give a sharp tone minimum in the telephone. The coil, tuned to a very high pitch, should be enclosed in a box surrounded by a poor conductor of sound, and placed at some distance from the bridge where the reading is to be made. The coil is driven by a storage cell of medium size. A platinum wire, or better, one of manganese alloy, which has a small temperature coefficient of resistance, is tightly stretched over the meter stick AB, which is carefully divided into millimeters. A rheostat W, whose total resistance amounts to 11,110 ohms, is convenient. The resistance vessel R, containing the solution and electrodes—the electrodes are cut from thick sheet platinum, and into each plate a stout platinum wire, about an inch in length, is welded. Glass tubes are sealed on to the platinum wires and electrode plates, by means of sealing glass. . . . These tubes pass tightly through a rubber cap, which fits over the glass vessel. They are filled to a convenient height with mercury, and electrical connection, established by means of copper wires, which dip into the mercury. One arm of the telephone, T, is thrown into the circuit between the rheostat and the resistance, and the other arm is connected with the bridge wire, by means of a slider. This is moved along the wire until that point is found at



which the hum of the induction coil ceases to be heard in the telephone. Let this be some point C, and let us represent AC by a, and BC by b, the resistance of the solution in the vessel R by r, and the resistance in ohms in the rheostat by w; then, from the principle of the bridge, we have

$$ra = wb$$

$$r = \frac{wb}{a}$$

But the conductivity of a solution, c, is the reciprocal of the resistance, r; therefore,

[1] P. Baumgarten. Beiträge zur Lehre von der natürlichen Immunität. Berl. klin. Wchnschr., No. 41, Oct. 9, 1899.

[2] Harry C. Jones. The Freezing-Point, Boiling-Point and Conductivity Methods.

$$c = \frac{a}{wb}$$

. . . A cell-constant, C, must be introduced and determined for each cell before it can be employed for conductivity measurements."

In calculating the molecular conductivity of a substance, its molecular concentration must be taken into account, but in these experiments this was not considered necessary. The results given in the tables express the conductivity simply as the reciprocal of the resistance, r, according to the formula

$$c = C\,\frac{va}{wb}$$

The material used in the experiments was dog-serum, obtained under proper aseptic precautions. In the first experiment the serum was heated from 24 to 70° C., and its conductivity tested at the following temperatures: 24°, 30°, 38°, 50°, 51°, 52°, 53°, 54°, 55°, 56°, 57°, 58°, 59°, 60°, 70°. It was then cooled to 38°, and its conductivity again tested. The material was kept at each of these temperatures long enough to ensure a constant reading, and the temperature was not raised above 70°, on account of the changes in concentration which would have occurred from evaporation.

Five more experiments were performed with serum taken from different dogs. The conductivity was tested at 24°, the material was then heated to 57° and kept at this temperature for one hour, after which it was slowly cooled to 24°, and the conductivity again tested, to discover if any change had taken place. The results of these experiments are incorporated in the following tables. The figures in each case represent the mean of three readings.

EXPERIMENT I.

24°	11.323	55°	19.283
30°	12.753	56°	19.643
38°	14.696	57°	19.881
50°	17.873	58°	20.133
51°	18.16	59°	20.41
52°	18.526	60°	20.73
53°	18.8	70°	23.253
54°	19.053	After cooling—	
		38°	14.743

The gradual increase in conductivity is, of course, due to the rise in temperature.

		Before heating to 57° C. for 1 hour.	After heating to 57° C. for 1 hr. and again cooling to 24° C.
Experiment II.	24°	11.436	11.466
Experiment III.	24°	11.786	11.763
Experiment IV.	24°	11.48	11.486
Experiment V.	24°	11.446	11.446
Experiment VI.	24°	10.546	10.56

The results of the above experiments go to prove that the alleged loss of bactericidal power in blood-serum heated to 57° is not due to any chemico-physical change which can be demonstrated by the conductivity method.

A CONTRIBUTION TO THE STUDY OF MALIGNANT TUMORS ARISING IN CONGENITAL MOLES.

By R. H. Whitehead, M. D., *Chapel Hill, N. C.*

(From the Pathological Laboratory of the Johns Hopkins University and Hospital.)

In 1893 Unna[1] announced his belief that melanotic malignant tumors which originate in pigmented moles should be classed as carcinomata. He based his opinion upon an examination of some tumors of this sort, and especially upon a study of moles obtained from newborn and very young children. According to him, the groups of pigmented cells commonly found in moles are derived from the epidermis during embryonic life or early childhood by being cut off from the interpapillary processes of the rete Malpighii, and afterwards losing their prickles and undergoing other metaplastic changes. He concluded, therefore, that melanotic tumors arising in moles are not sarcomata, but carcinomata.

Since, at that time, it was generally held that the so-called nævus cells were of endothelial origin, Unna's statement aroused considerable opposition. Green[2] denied the epidermal genesis of the nævus cells, and pointed out that there is no relation between the amount of pigment in them and that in the epidermis—that it may be present in either situation while absent from the other.

Then Bauer,[3] a pupil of Ribbert, investigated the subject, and reached conclusions quite the opposite of those of Unna, even after examining Unna preparations. He convinced himself that the nævus cells were of endothelial origin, and stated, furthermore, that the individual cells in the groups were separated from one another by a fine fibrous network, and that they were frequently branched so as to resemble stellate connective-tissue cells.

Lubarsch[4] stated that he had examined a considerable number of moles in newborn and young children, and had

[1] Unna, P. G. Nævi und Nævocarcinome. Berl. klin. Wchnschr., 1893, XXX, 14.

[2] Green, L. Ueber Nævi pigmentosi. Virchow's Archiv, 1893, CXXXIV, 331.

[3] Bauer, C. Ueber endotheliale Hautwarzen und ihre Beziehungen zum Sarcom. Virchow's Archiv, 1895, CXLII, 407.

[4] Lubarsch-Ostertag. Ergeb. d. allg. Pathol., etc., Wiesbaden, 1896, Bd. II, S. 379.

not been able to detect any correspondence between the nævus cells and those of the epidermis.

Unna, however, did not fail to find supporters. Delbanco,[5] as the result of his study of two moles, stated that the interpapillary processes of the epidermis are frequently in direct connection with the groups of nævus cells, and that, owing to proliferation of the stroma of the mole, numerous epidermal cells are separated off into groups and afterwards displaced into the lymph vessels.

Kromayer[6] rejected Delbanco's conclusion that the nævus cells are contained in lymph vessels, but agreed with him and with Unna in deriving them from the epidermis. This investigator describes in the moles of infants cyst-like spaces filled with cells containing vesicular nuclei. They are situated in the epidermis, between the epidermis and the subjacent connective tissue, or entirely within the latter. He thinks that all of these groups of cells become enclosed by connective tissue later on, and that then the cells throw off fibres, until finally little is left of the individual cells save nuclei closely applied to fibres—that, in fine, the epithelial are metamorphosed into connective-tissue cells.

Lubarsch,[7] in a critical review of the work done up to that time, expressed the opinion that the researches of Unna, Delbanco, and Kromayer were individual interpretations of microscopic pictures rather than objective descriptions of appearances actually observed, and that their illustrations were susceptible of more than one interpretation. Thus, he claimed that Kromayer's picture representing nests of nævus cells in the epidermis could be reproduced by oblique sections of the skin in conditions characterized by elevations of the epidermis, as the result of growing or proliferating papillæ. Nor was he willing to accept Kromayer's metaplasia of epithelial into connective-tissue cells, holding that the law of the legitimate succession of differentiated cells was too well established to be surrendered on such proof as Kromayer presented. He criticized also the method with which Kromayer worked, and was not convinced by his original preparations. Still, he was unwilling to deny the possible existence of epithelial nævi.

A little later Scheuber[8] made serial sections of several pigmented moles, and convinced himself that Unna's view as to the origin of nævus cells was correct.

Recently Gilchrist[9] has made an investigation of the subject, and, from the study of a pigmented mole in an infant, arrived at the conclusion that the nævus cells are developed in the way described by Unna.

Finally, Schalek[10] has studied some pigmented moles and melanotic tumors of the skin, and has satisfied himself of the correctness of Unna's views.

In the midst of such difference of opinion one finds it difficult to reach a definite conclusion as to the nature of the nævus cells; but the pictures of Scheuber and of Gilchrist are, to say the least, exceedingly suggestive, and one may fairly be permitted to hold the view that in some moles, at least, the groups of cells are modified epithelial cells of epidermal origin. Should a tumor spring from such cells, we should, naturally, expect it to follow the type of carcinoma. This expectation, however, is not always realized. Unna,[11] indeed, states that all of these tumors which he has studied presented the structure of alveolar carcinoma (carcinoma simplex). On the other hand, the nine tumors of this class which I have been able to examine, had that histological structure which most pathologists have agreed to call alveolar sarcoma, and were so pronounced by competent observers. While we may well hesitate to be dogmatic in such matters, yet one is reluctant to regard as a carcinoma a tumor which presents so many characteristics of the sarcomata.

The following cases are reported not so much with the hope of throwing new light upon this vexed question as rather to call attention to the fact that tumors may spring from congenital moles which represent the same processes as those going on in the melanotic tumors, with the exception that they totally lack true melanotic pigment.

Case 1.—The subject of this tumor was a white man aged 47 years. He had noticed, as long as he could remember, a "black mole" on the front of his right forearm a little above the wrist. For the last few weeks this had been enlarging rapidly, so that when I saw him there was in the situation mentioned a perfectly black tumor, conical in shape, and about 2 cm. high. The color was due largely to clotted blood, with which the tumor was encrusted, owing to frequent hemorrhages. The growth was removed by incisions carried widely into apparently healthy tissues. Eight months afterwards I learned that he had died "with tumors all over him." They were estimated as at least 200 in number, were situated in and beneath the skin, and varied in size from that of a pea to that of a hen's egg. Towards the end of his life he suffered much from frequent painful micturition, and on several occasions passed in his urine fleshy masses believed by his medical attendant to be pieces of tumor.

On section the tumor was deeply pigmented in places, and was spongy and friable, tending to crumble to bits when handled at all roughly. It arose by a broad, short pedicle a little more than one cm. thick.

In longitudinal sections through the pedicle the latter is seen to be formed by dense fibrous tissue containing sweat

[5] Delbanco, E. Epithelialer Nævus. Monatsh. f. prakt. Dermat., 1896, XXII, 105.

[6] Kromayer, E. Zur Histogenese der weichen Hautnævi. Dermat. Ztschr., 1896, III, 263.

[7] Op. cit., S. 591.

[8] Scheuber, A. Ueber den Ursprung der weichen Nævi. Arch. f. Dermat. u. Syph., 1898, XLIV, 175.

[9] Gilchrist, T. C. On Malignant Growths Arising from Pigmented Moles. Journ. Cut. and Genito-Urin. Dis., 1899, XVII, 117.

[10] Schalek, A. Contribution to the Histogenesis of Melanocarcinoma of the Skin. Journ. Cut. and Genito-Urin. Dis., 1900, XVIII, 145.

[11] Unna, P. G., op cit.

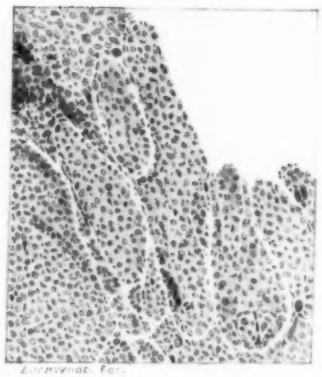


FIG. 1.—Shows structure of the tumor in Case I.

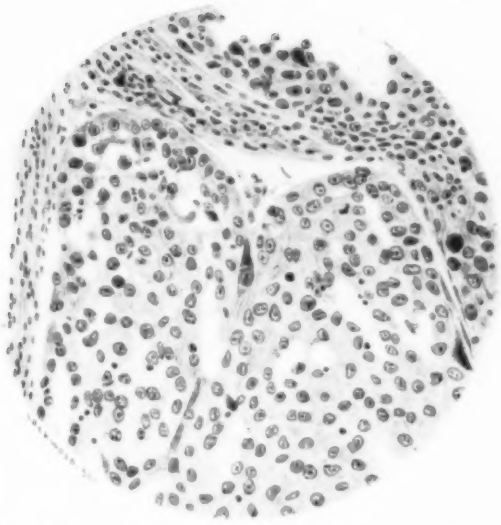


FIG. 2, CASE I.—Shows the intraalveolar reticulum.

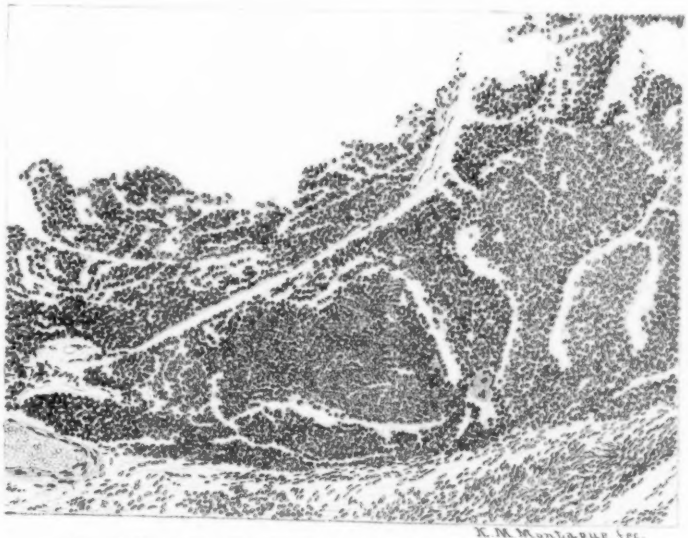


FIG. 3, CASE II.—Portion of a cell-mass of the first variety.

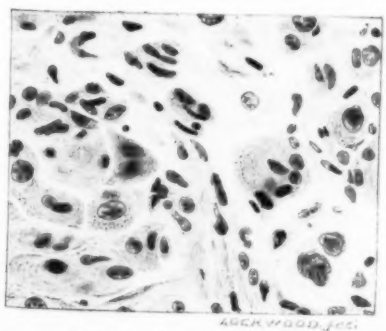


FIG. 4, CASE II.—Portion of a cell-mass of the second variety.

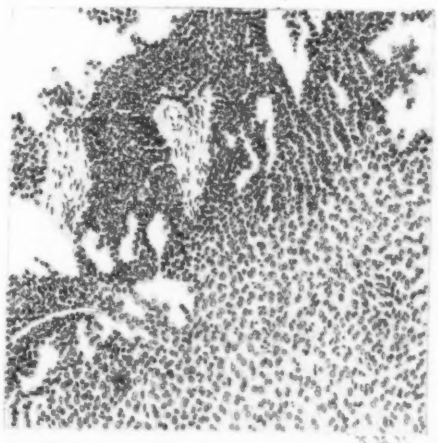


FIG. 5, CASE II.—Transition from a mass of the first to one of the second variety.

and sebaceous glands and a few hair roots. Proceeding towards the tumor proper, many young capillaries are encountered containing numerous polymorphonuclear leucocytes and surrounded, here and there, by groups of small round cells. In this region pigment begins to appear as small masses of a yellow-brown color. In some cases these masses are contained in branched cells; in others I am unable to decide whether they are intra- or extracellular in situation. Near the pedicle the arrangement of the tumor is alveolar in character, though the stroma soon becomes very scanty, the walls of the alveoli being quite delicate and furnished by a few spindle-shaped cells. The cells within the alveoli are, in the main, large and polygonal; their nuclei are fairly constant in size and appearance, being vesicular with nucleoli and grains of chromatin. Cells with several or budding nuclei are frequently seen. In certain alveoli from which some of the cells have been removed by shaking, it can be seen that the cells are separated from one another by a very fine reticulum, which appears to consist in large part of processes from the cells themselves. Many of the cells contain pigment in the form of yellow-brown grains. Farther towards the periphery of the tumor the alveolar is succeeded by what may be termed a diffuse arrangement of the cells. Here the stroma, reduced to a minimum, is represented only by a few parallel rows of endothelial cells running here and there through the large masses of cells. It is difficult in this region to detect any intercellular substance; occasionally one sees cells with fibrillar processes. Very common are exceedingly large cells, spherical and multinucleated, containing many granules of pigment. The superficial portions of the tumor are inflamed or necrotic, and infiltrated with blood. The areas still living consist of large vascular spaces lined by endothelium and surrounded by masses of tumor cells. The epidermis near the pedicle is thickened, but no connection can be made out between it and the tumor proper. In other situations the epidermis has broken down before the invading masses of tumor cells, which grow through and project beyond it. It has entirely disappeared from over the greater portion of the surface of the tumor. In the thickened epidermis a few epithelial pearls were noticed, some of which contained pigment. The tests for iron-containing pigment resulted negatively.

Here we have a typical example, in an advanced stage, of the malignant melanotic growths which spring from the nævus cells of congenital moles—the nævocarcinomata of Unna, or the alveolar melanotic sarcomata of most authors.

CASE 2.—This tumor was obtained, through the kindness of Dr. C. S. Mangum, from a white woman 50 years old. She consulted Dr. Mangum concerning a large mole situated over the inferior angle of the left scapula. It had been present "all her life," but only recently had been enlarging. Dr. Mangum thought best to remove the mole, especially as there were evidences of beginning ulceration. The subsequent history, unfortunately, could not be fully obtained. It was learned, however, that the wound made by the operation never healed, and that the lymph nodes in the left axilla soon became enlarged. About eighteen months after the operation she was considered by her family physician to be dying of a malignant tumor of the uterus.

The tumor is about 2 cm. long, and 1 cm. thick. It presents the macroscopical appearances of soft papilloma, its surface being corrugated. It possesses a short, narrow pedicle. On section it is seen to be pigmented in streaks of a dark slate color.

In sections made through the center of the mole including the pedicle, the latter is found composed of fibrous tissue; its arteries are thickened, and there are some patches of small round cells. In these sections the structure is quite suggestive of carcinoma simplex. There are variously shaped alveoli, for the most part long and narrow, whose walls are thick and formed by dense fibrous tissue with scanty spindle cells. The cells within the alveoli are packed closely without visible intercellular substance. They are regular in size and appearance, being rather small polyhedral cells with pale vesicular nuclei. This area, doubtless, consists of normal mole tissue.

Sections made through the other portions of the tumor, however, present a different picture. The most prominent feature is furnished by large, more or less round collections of cells surrounded by capsules of dense fibrous tissue. They are not all alike, but may be divided into two varieties. The more numerous ones are composed, in the main, of small polygonal cells with deeply staining nuclei, though occasionally one sees a very large cell with more than one nucleus. The primary mass of cells is subdivided into much smaller masses by a spindle-celled connective tissue, which runs in from the surrounding connective tissue, and conveys vessels. In most cases this tissue is quite scanty, and often the subdivisions seem to be separated only by narrow cracks, the boundaries of which are the tumor cells, though sometimes a few spindle cells can be seen bordering them. No intercellular substance can be made out between the cells in the subdivisions. In some of the masses the thickness of the connective tissue septa is much greater than in those just described, and then an appearance is produced somewhat like that described in sections through the center of the tumor.

The cell masses of the second variety are not so numerous as those of the first, and are not so sharply circumscribed. The cells composing them are, for the most part, very large and round, and many of them contain more than one nucleus. They are separated from one another by a delicate reticulum, which frequently holds deeply staining nuclei; or several cells may be shut off into small groups by portions of the reticulum. As a rule, the cells towards the periphery of these masses tend to assume the spindle shape, and gradually fade away into the surrounding connective tissue. Areas are observed where a mass of the first variety is passing by gradual transition into one of the second variety. Moreover, in the case of both varieties, columns of cells advance into the surrounding stroma, where they usually tend to the spindle shape.

The stroma of the tumor is furnished by a central trunk of fibrous tissue, which gives off branches here and there to surround the cell masses alluded to. It conveys many blood-

vessels, around which are some patches of small round cells and many plasma cells, and contains scattered, long, narrow spindle nuclei. In several places this tissue is lost in diffuse masses of large spindle-shaped cells, for which it seems to form an intercellular substance.

The surface of the tumor is covered everywhere by epidermis, which is necrotic over a considerable extent of the tumor. Where the epidermis is intact, it is seen to be very thin—it is reduced to two or three layers of cells—and is separated from the subjacent tissue by distinct lines of connective tissue. Some epithelial pegs project from the epidermis, but they, too, are very thin, and show no connection with the tumor cells. The pigment was found chiefly along the course of the blood-vessels and in the most superficial parts of the growth, where hemorrhages had occurred. Much of it responded positively to the ferrocyanide of potassium test, and the remainder was amorphous hæmatoidin contained largely in polymorphonuclear leucocytes.

In this case, it would seem, the processes which occur in the malignant melanotic tumors are undoubtedly going on—the development of a malignant tumor from the nests of nævus cells in a congenital mole, but with the exception that true melanotic pigment is not present. *A priori*, we should expect to find such tumors, for Green [12] has shown that the nævus cells are not always pigmented, nor are tumors which arise in melanotic tissues invariably melanotic, but I have not been able to find the records of a similar case. Unna [13] hints at the possible existence of such growths, but makes distinct mention only of melanotic tumors.

[12] Green, L. op. cit.

[13] Unna, P. G. Die Histopathologie der Hautkrankheiten. Berl., 1894, pp. 746-752.

INORGANIC FERMENTS.[1]

By Harry C. Jones, Ph. D.,

Associate Professor of Physical Chemistry Johns Hopkins University.

A paper bearing this title has recently appeared by Bredig and Müller von Berneck.[2] The authors first point out certain analogies between the action of ferments and the contact action of metals. Alcohol is oxidized to acetic acid by the oxygen of the air as well by finely divided platinum as by the organic ferment *mycoderma aceti*. Calcium formate is decomposed into calcium carbonate, carbon dioxide and hydrogen, not only by certain bacteria, but by finely divided iridium, rhodium, or ruthenium. Finely divided platinum, palladium, iridium, osmium, etc., have the power of inverting cane sugar, like invertose.

The above relations are, however, only analogies. To determine whether there is any close relation between the action of organic ferments and finely divided metals, some reaction effected by both classes of substances must be carefully studied.

The reaction chosen by the authors of this paper is the decomposition of hydrogen dioxide. This reaction is effected by all organic ferments and, also, by finely divided metals, in the sense of the following equation:

$$H_2O_2 = H_2O + O$$

The metal chosen was platinum, and a colloidal solution of this substance was prepared as follows: Two platinum wires about 1 mm. in diameter were immersed in a vessel containing very pure water. These were placed at a convenient distance apart, and a current of from 8 to 12 amperes and 30 to 40 volts passed between them. There was thus formed an arc between the platinum poles beneath the surface of the water. Platinum was torn off from the cathode in a very finely divided condition, and quickly gave a blackish-brown color to the surrounding water. The liquid was then rapidly filtered through a folded filter to remove any larger particles of platinum which may have been torn off. The colloidal solution of platinum is a clear, dark brown liquid, which, when examined under the microscope, appears to be perfectly homogeneous. The platinum particles must, therefore, be of an order of magnitude less than a wave-length of light. The amount of platinum contained in the solution could be easily determined by treating with a little concentrated hydrochloric acid. The platinum was precipitated and could be filtered off and weighed. The decomposition of hydrogen dioxide by means of this liquid was then studied.

There are two striking characteristics of the action of organic ferments. First, a very small amount of the ferment can effect a large amount of reaction. Second, the ferment itself very probably does not enter, as such, into the reaction.

Bredig and von Berneck studied the action of the colloidal platinum with reference to these two points. They found that a gram-atomic weight of platinum in about 70,000,000 litres of water would appreciably decompose hydrogen dioxide. This showed that an almost infinitesimal amount of the metal was capable of effecting the reaction. Similar results were obtained with other metals and metallic oxides, such as manganese dioxide, cobalt oxide, copper oxide, lead dioxide, etc. The first point of resemblance between the action of organic ferments and of these inorganic substances is thus evidently very close.

The method of testing the second point, whether the metal enters into the reaction, is at first sight not so obvious. Indeed, there is no strictly chemical method for deciding this

[1] Presented to the Johns Hopkins Hospital Medical Society.

[2] Ztschr. phys. Chem. (Jubelband zu van't Hoff), 31, 258.

point. The fact that the platinum remains in the solution after the reaction in the same condition as before, is no proof that it has not entered into the reaction and then came out again as such. There is, however, a physical-chemical method by means of which this problem can be easily and satisfactorily solved. If the platinum does not enter into the reaction but acts only by contact, it is evident that there is only one substance reacting. Such reactions are termed monomolecular. If the platinum does enter into the reaction there are two substances reacting, and such a reaction is termed bimolecular. We can distinguish very readily between mono- and bimolecular reactions. Without entering too far into the mathematical side of the problem, it has been shown from the law of Mass Action that for reactions of the first order the expression connecting the time during which the reaction has proceeded with the amount of substance transformed is:

$$\frac{1}{\vartheta} \ln \frac{A}{A-X} = C$$

in which ϑ is the time, A the original amount of substance, X the amount decomposed, and C is a constant.

Similarly, for reactions of the second order we have:

$$\frac{1}{\vartheta} \frac{X}{A-X} = C$$

in which the symbols have the same significance as above.

To determine the order of the reaction it is only necessary to decide experimentally between these two equations. This is quite simple. It is only necessary to know the amount of hydrogen dioxide with which we start, (A) and to measure the amount transformed (X) in any given time (ϑ). Then substitute these values in the above equations and obtain C. Having done this for any given time, allow the time to vary and measure X for the new time. Again calculate C. Repeat this process for a number of values of ϑ and calculate C in each case from both equations. If the values of C are a constant for varying values of ϑ as calculated by the first equation the reaction is one of the first order. If, on the contrary, C comes out a constant as calculated by the second equation the reaction in question is one of the second order.

In the reaction with which we are dealing, C, as calculated by the first equation, is a constant, and hence the decomposition of hydrogen dioxide by platinum is a monomolecular reaction. The platinum, therefore, does not enter into the reaction, and we have established the second point of resemblance between the action of organic ferments and that of finely divided platinum.

The most striking analogy between the action of the colloidal platinum and of organic ferments still remains to be considered. It is well known how sensitive organic ferments are to the action of certain poisons. The same phenomenon is manifested by the solution of platinum. Thus, a gram-molecular weight of hydrocyanic acid in one million litres of water reduces, quite appreciably, the action of the platinum solution on hydrogen dioxide. Hydrogen sulphide has also a poisonous action. A gram-molecular weight of the gas dissolved in 345,000 litres of water diminishes the velocity with which the colloidal platinum will decompose hydrogen dioxide, and a solution of hydrogen sulphide ten times as concentrated as the above, reduces the velocity of the reaction nearly to zero. Carbon bisulphide and mercuric chloride also exert a poisonous influence on the solution of platinum, reducing the rate at which it will decompose hydrogen dioxide, and, if present in sufficient quantity, entirely preventing the reaction.

Whatever conclusions may be drawn from this work the fact cannot be disregarded that there are a number of very striking analogies between the action of finely divided platinum and that of organic ferments. While it seems to the reviewer a little premature to draw final conclusions, yet enough has already been done to show that this is a very promising field for investigation. If it should be shown that these analogies are deep-seated, then, work of this kind cannot fail to throw light on the nature of fermentation and similar processes. Metallic platinum in the form of a colloidal solution is one of the simplest substances known to the chemist. Organic ferments are in general very complex. If the action of the two is analogous, then, by studying the action of the simpler substance much light may be thrown on the *modus operandi* of the more complex enzymes.

It is impossible to say at present to just what this work may lead. It is certainly an important step in a direction which is full of promise, and is another example of the way in which physical chemistry is throwing light, not only on chemical and physical problems, but also on biological.

THE STERILIZATION OF CATGUT.

BY G. BROWN MILLER, M. D.,

Resident Gynecologist The Johns Hopkins Hospital.

The value of absorbable suture and ligature materials has been for years so apparent that much work has been done to secure one which would answer the conditions imposed by the requirements of aseptic surgery. Catgut is the cheapest and best of such materials. Its properties are so well known that an enumeration of them here would be superfluous. The principal objection to its use as sutures or ligatures is the difficulty experienced in its sterilization.

In the spring and summer of 1899 I tested several methods which seemed to me the most promising of the many in use. My endeavor was to secure a method of catgut sterilization so simple in its technique that it could be generally adopted. There are two conditions which must be fulfilled and several which it is desirable to meet in the preparation of catgut for surgical purposes. The first essential condition is, that the *sterilization* must be perfect. Not only must the pyogenic cocci be killed, but the spores of the most resistant bacteria, whether pathogenic or not, must likewise be destroyed by the sterilizing process. It is not sufficient to have a method which apparently gives good clinical results. In the literature of the subject we find many methods which have been extensively used and the results clinically declared good, which careful bacteriological tests prove to be untrustworthy. The reason of the discrepancy is probably the following: The method of sterilization destroys the least resistant bacteria and inhibits to a certain extent the growth and development of the more resistant. When such catgut is placed in tissue which is well supplied with blood the bacteria and their spores in their weakened condition are destroyed by the tissue juices, leucocytes, etc. Place such catgut, however, in conditions which favor the development of these bacteria, as in a large blood-clot or in tissue cut off from its blood supply, and we may easily conceive of a very different result. The bacteria or their spores finding here conditions favoring their development and multiplication may grow as on the common nutrient media in the laboratory and having acquired sufficient powers of resistance may invade the human organism. Bacteria which are considered non-pathogenic may cause the decomposition of such a clot and the absorption of the products so formed may act to the detriment of the patient.

In my experiments I have seen the spores so acted upon that only after several days would they slowly develop into bacteria when placed in *bouillon* at a favorable temperature. Placed immediately upon nutrient agar or gelatin they would not grow, but after their development in bouillon, when transplanted to these media, they would grow readily. The conscientious surgeon would not to-day use any suture material which is not certainly sterile.

The second essential condition is that the catgut must be strong and pliable. After fulfilling these essential conditions the ideal method of sterilization should fulfil others, viz., the method should not require too much time nor be too troublesome, the catgut should not be swollen, it should be kept in some manner where it is not easily contaminated, it should be easily transportable, and it should be free from poisonous or irritating chemical substances.

The various methods in use depend upon heat, chemical agents, or a combination of the two as a means of sterilization. Heat is an ideal method of sterilization so far as the destruction of the bacteria is concerned. A sufficiently high temperature will destroy all bacteria known to us and leave no extraneous irritating substances in the material sterilized. The problem is the method of applying the heat so as not to impair too much the strength and pliability of the catgut. It has been found that catgut, which has been thoroughly dried, will stand a high degree of heat without much injury. Upon this principle depends the "Dry Heat" and the "Cumol" methods of sterilizations. Chemical agents, on the other hand, are uncertain in their bactericidal properties and investigators are becoming daily more sceptical as to these properties. Soak contaminated silk or catgut in a carbolic acid or mercuric chloride solution and place these materials on nutrient media without washing out or neutralizing these chemical agents and enough of the carbolic acid or mercuric chloride may remain in the strands of silk or catgut to prevent the development of the bacteria. Neutralize or wash out thoroughly the chemical agents and the microorganisms will grow. Upon this depends the apparently favorable bacteriological tests of many untrustworthy methods. Reppert first called attention to this. The agent used also remains in the catgut and may do harm where much of the material is used.

In looking over the methods of catgut sterilization in more general use the following ones suggested themselves as the most promising: Schäffer's, Vollmer's (Formalin), Reverdin's (Dry Heat), Krönig's (Cumol), Sweetnam's.

I will give a short description of each and my tests bacteriologically in a tabulated form.

Schäffer's Method.—This method, which is one of the simplest in its technique, is as follows: The catgut without previous preparation is boiled in the following solution: absolute alcohol, 85 cbcm.; distilled water, 15 cbcm.; pure mercuric chloride, .5 grm. At least 250 cbcm of this solution is placed in an apparatus devised by Schäffer along with the catgut and by means of a water bath brought slowly to the boiling point of the liquid. After 15 minutes vigorous ebullition the alcoholic solution is allowed to cool 5-10 minutes, the catgut is removed and placed in 95 per cent alcohol, and it is ready for use. Schäffer says in his article in conclusion, that the catgut is absolutely sterile, that it loses none of its strength, that the sterilization takes only 30-40 minutes, and that the apparatus cost only 15 marks. He has written an exhaustive article upon the subject of catgut sterilization and in it reviews many other methods, all of which he regards as faulty. I gave his method a thorough bacteriological test, using the utmost care in carrying out his directions. It is necessary to render the mercuric chloride remaining in the catgut after sterilization inert as regards its action upon the bacteria used. To do this I introduced the ligatures into test tubes containing sterile water, and conducted into this through a sterile glass tube the gas obtained by heating ammonium sulphide. The mercury remaining in the ligatures was precipitated as a sulphide which is inert in its action on bacteria. This was afterwards washed out in sterile water and the ligatures were finally placed in bouillon tubes and these put in the laboratory incubator. The table which follows shows the results obtained. I will briefly state here the method used by me in obtaining resistant spores. The bacteria used were obtained from the Bacteriological Laboratory of the Johns Hopkins Hospital through the kindness of Dr. Harris.

I chose the following bacteria, *i. e.* Bacillus Anthracis, Bacillus Subtilis, Bacillus Megatherium and a resistant Potato Bacillus. The latter was one which grew on some of my potatoes after the usual sterilization. These bacteria were placed upon slant-agar and potato and allowed to grow for three or more days at a temperature 28°-30° C. Coarse silk threads, which were used in the tests as more convenient than catgut, were rubbed thoroughly into the cultures which invariably contained numerous spores and were then subjected to the sterilizing processes. After neutralizing or washing out the chemical ingredients used in the various methods the sutures were dropped into bouillon tubes and these were placed in the incubator. In most of my experiments no effort was made to keep the bacteria apart and in some cases I was satisfied to obtain a growth which contained at least one of the bacteria used. However, as shown in the tables, I did in some cases use pure cultures of the bacteria. This can be seen by referring to the tables where the microorganisms are indicated by the first letter of their names, as A—Anthrax, S—Subtilis. P—Potato Bacillus and M—Megatherium. A glance at the following table will show that in every trial of the method a growth was obtained from the sutures which had been subjected to Schäffer's sterilizing process. In four tests, where I used anthrax alone, this microorganism was obtained in pure culture. The method must in consequence of these results be regarded as thoroughly unreliable. Anthrax in catgut has caused in more than one reported case a fatal infection. Within the past six months a Chicago surgeon has told me of two of his patients who were operated upon the same day, dying of anthrax infection which was caused by the catgut used in the operations.

SCHÄFFER'S METHOD.

Date.	Bacteria.	Result.
April 12th..	A. S. P. M.	Growth.
" 19th..	"	Growth. (Anthrax and subtilis isolated.)
" 24th..	"	Growth.
No. 1. " 27th..	"	"
No. 2. " " ..	"	"
" 28th..	"	" (Anthrax and subtilis isolated.)
May 4th..	"	"
" 15th..	A.	" (Pure culture of anthrax.)
" 24th..	A.	" (Pure culture of anthrax. Animal inoculation.)
" 26th..	A.	" (Pure culture of anthrax. Animal inoculation.)
June 11th..	A.	" (Pure culture of anthrax. Animal inoculation.)

Kossmann's Method.—Kossmann takes ordinary catgut and immerses it in a 2 per cent formaldehyde solution for 24 hours. It is then washed two or three times in Tavel's solution: Sod. Chlor., 7.5 parts; Sod. Carbon., 2.5 parts; Dist. Water, 1000 parts; with gentle shaking to remove the formaldehyde. The catgut is kept in the same solution. He claims that the catgut is sterile, strong, and swells very little. Schäffer tested this method repeatedly and asserts as a result of his experiments that the catgut is not certainly sterile. The method has so much to recommend it in its simplicity that I tested it thoroughly. The catgut loses considerably in strength, swells to a certain extent and my bacteriological tests, while at times negative, showed enough positive results to prove that one cannot recommend the method. Schäffer made the assertion that the reason that Kossman and Vollmer, who recommended the method, got negative results when testing the method bacteriologically was because they did not neutralize the formalin, and enough of this remained in the threads to inhibit the growth of the bacteria or the development of the spores. He took some sutures, which had been inoculated with resistant bacteria, subjected them to the action of formalin and placed them without this neutralization in bouillon. They remained in this media eight days without the development of the bacteria. He then neutralized the formalin with dilute ammonia and the bacteria readily developed. In the experiments given in the following table the formalin remaining in the sutures was neutralized by means of ammonia gas driven off by heating aqua ammonia and conducted into the test tube through a sterile bent glass tube.

KOSSMANN'S METHOD.

Date.	% Formaldehyde.	Time exposed to formulin.	Bacteria.	Result.
April 14th...	2%	24 hours.	A. S. M. P.	Negative.
" 19th...	2%	24 "	"	Negative.
" 20th...	2%	24 "	"	Growth.
" 25th...	2%	24 "	"	"
" 28th...	2%	24 "	"	"
May 1st...	2%	24 "	"	"
	4%	24 "	"	Negative.
" 3rd...	2%	24 "	"	Growth.
	4%	24 "	"	Negative.
" 16th...	2%	24 "	A. S.	Negative.
	4%	24 "		"
" 22nd...	2%	24 "	A. S.	"
	4%	24 "		"
June 9th...	4%	24 "	A. S. M.	"
" 12th..	2%	24 "	A. S.	Growth.
	4%	24 "		Negative.
" 19th...	2%	24 "	A. S. M.	Growth.
	4%	24 "		Negative.
" 21st...	2%	24 "	A.	Negative.
" 23rd...	2%	24 "	A. S. M.	Growth.
" 26th...	2%	24 "	"	"
" 29th...	2%	24 "	"	Negative.
July 7th...	2%	24 "	"	"

I tried, in addition to the above experiments, dipping the threads in oil after inoculation and before sterilization, and in every instance got positive results. This was to be expected as the oil prevented the formalin from coming in contact with the bacteria. It is an additional objection to Kossmann's method. As a result of my experiments the sterilization of catgut by this method I regard as untrustworthy and therefore should not be employed.

Sweetnam's Method.—Sweetnam's method consists in heating the catgut in sweet almond oil containing 10 per cent of carbolic acid over a water bath at a temperature of 212° F. for one hour, and preserving the catgut in the same solution. The method has much to recommend it in its simplicity and the short time required in carrying it out. I give the table of tests below. One will notice that some of the tests gave

positive results, and if I could have found some means of neutralizing all of the carbolic acid or freeing the threads from the carbolized oil there would undoubtedly have been more. Attempts to wash the oil which contained the carbolic acid from the silk were to a large extent futile, and a sufficient quantity of the antiseptic probably remained in every instance to inhibit to a certain extent the development of the spores. Leaving this out of consideration a sufficient number of positive results were obtained to make us regard the method as unreliable.

SWEETNAM'S METHOD.

Date. 1899.	Bacteria.	Treatment to rid threads of carbolized oil.	Results.
June 10th..	A. S. M.	3 rinsings in sterile water.	Negative.
" 13th..	"	4 " " "	Growth.
" 14th..	"	4 " " "	Negative.
" 22nd .	"	Allowed to stand 24 hours in sterile water; rinsing.	Growth.
" 26th..	"	24 hrs. in water, and 3 rinsings.	Growth.
" 28th..	"	24 " " " "	Negative.
July 5th..	P. A. S. M.	1 rinsing in NH_4O–3 in sterile water.	Growth.
" 6th..	"	2 rinsings in NH_4O and 1 in sterile water.	Negative.
" 8th..	"	2 rinsings in NH_4O and 3 in sterile water.	Negative.

I did not make as many tests of this method as of the others because I could not find a satisfactory method of freeing the sutures from the oil.

The Dry Heat Method.—This method was originated by Reverdin and used subsequently by Döderlein, Benckiser, Boeckmann and others. It consists in heating the catgut slowly in a dry air sterilizer to 150° C., and keeping it at this temperature for 2 hours. I found it very difficult with an ordinary laboratory sterilizer to regulate the heat, and the catgut was apt to lose its strength. Schäffer had no criticism to offer so far as the bacteriological provings were concerned, and my experiments, as can be seen in the table, were satisfactory. The catgut was not as strong and pliable as the Cumol catgut and the method requires closer attention unless one has a better method of regulating the heat than can be had with an ordinary dry air sterilizer. The following table shows the time of drying and the temperature at which the sutures were heated:

THE DRY AIR METHOD.

Date. 1899.	Time of drying.	Time of heating.	Bacteria.	Results.
July 3	3 hrs. to 140° C.	½ hr. at 140° C.	A. S. P. M.	Growth.
July 5 2 exp.	1½ hrs. to 140°	½ hr. at 140°	"	"
July 6 2 exp.	1¾ hrs. to 140°	1 hr. at 138°-142°	"	Both negative.
July 8 2 exp.	1¾ hrs. to 140°	1 hr. at 138°-140°	"	Growth in both.
July 7 2 exp.	¼ hr. to 140°	50 mins. at 140°	"	" "
July 10 2 exp.	2 hrs. to 140°	1 hr. at 138°-143°	"	" "
July 12 2 exp.	3 hrs. to 140°	5 hrs. at 138°-140°	"	Both negative.
July 13 2 exp.	2½ hrs. to 140°	1½ hrs. to 138°-147°	"	" "
July 14 2 exp.	3 hrs. to 140°	4 hrs. to 140°	"	" "
July 17 2 exp.	2 hrs. to 140°	1½ hrs. at 135°-150°	"	" "
July 21 2 exp.	1 hr. to 140°	2 hrs. at 140°-145°	"	Growth in one.
July 22 2 exp.	2 hrs. to 140°	2½ hrs. at 140°-142°	"	Both negative.

One sees that in the above experiments in almost every case where the threads were heated for 2 or more hours at a temperature above 140° C. the threads remained sterile. Reverdin's method calls for 2 hours at 150° C. The method must therefore be regarded as satisfactory from a bacteriological standpoint.

The Cumol Method.—The Cumol method of catgut sterilization first used by Krönig and modified by Clark and Miller proved to be perfect as regards its germicidal properties, and when properly carried out gave strong, pliable catgut. I give here an account of the method as used in the Johns Hopkins Hospital and append a table of bacteriological provings: "Cut the catgut into desirable lengths, 35-40 cm., wind it into small coils or rolls each containing eight to ten strands (It should not be tied or only loosely). It is then heated slowly (at least two hours) to 85° C. in a dry air sterilizer and kept at this temperature approximately for two hours. After thorough drying it is placed immediately in a metal vessel containing Cumol (which should cover the catgut), and this is heated over a sand bath to 160-165° C. and kept at this temperature for one hour. The Cumol is then decanted and the excess left in the catgut is evaporated by leaving the vessel over the sand bath for one hour longer, the flame having been removed. The rolls of catgut are then placed in wide-mouthed sterile test tubes, a few rolls in each tube, and these are kept in a covered vessel and used as desired. A convenient apparatus has been devised by Clark which could be improved by leaving off the glass indicating tube. The principal points to be observed are as follows: the catgut must be perfectly dried before subjecting it to the high temperature of boiling Cumol, and care must be taken that the vapor of the Cumol, which is heavier than air, does not come into contact with the flame or red hot metal. If the catgut is not perfectly dried it will become brittle on boiling. To prevent the Cumol from taking fire the sand bath must be a wide one, extending at least 3-4 inches beyond the flame on all sides, and the vessel containing the Cumol should have a tightly fitting top with a corked opening for the thermometer, and an escape tube, by means of which the gaseous Cumol can be conducted away from the flame. Any device by which the vapor is prevented from rolling over the sides of the vessel will answer. It is well to place the catgut before drying in a suitable wire basket and surround it with filter paper. The basket with its contents is transferred from the drying apparatus to the Cumol. This device prevents the catgut from coming in contact with the sides of the metal vessel. The method of Cumol sterilization has been used for five years in the Gynecological Department of the Johns Hopkins Hospital with perfectly satisfactory clinical results. The objections to its use are the time and care required in carrying it out. The cost is relatively small, as very little Cumol is lost each time and the liquid can be used repeatedly."

The No. 3 catgut, the heaviest used by us, is completely absorbed in the skin in ten days and loses largely its strength in 6-7 days. For ordinary purposes this time is sufficiently

long, but in the closure of herniæ, abdominal incisions, etc., a longer time of absorption is desired. I have taken advantage of the well known fact that catgut soaked in formalin requires a longer time for absorption to overcome this objection. The No. 3 catgut is soaked in a 4 per cent formaldehyde or a 10 per cent formalin solution for ten hours; it is then washed several hours in running water, dried, and sterilized by the Cumol method. Catgut so treated is as strong as ordinary catgut and rougher on its surface, which is no objection in tying. I have tested the time required for its absorption in a large number of cases during the past eight months and find it to be from 14-18 days. By using stronger solutions of formalin or by exposing the catgut longer to its action this time can be increased. If soaked too long or if the formalin is not thoroughly washed out the catgut loses in strength. My method is, to take the large rolls of catgut as they come from the dealer, cut the silk threads which bind them, place them on a cylinder which they fit loosely, and soak them in the formalin. After ten hours they are removed from the formalin and placed in running water over night. They are then wound on a loose, wide gauze roller bandage and dried in the sun or before a hot air draught. The process after that is the same as described in the Cumol method.

The following table shows how absolute the sterilization is in the "Cumol Method." The method calls for one hour at the required temperature, while in every instance in ten minutes the same bacteria which were used in the other experiments were completely destroyed. Until some simpler method is discovered which gives equally as good bacteriological results the "Cumol Method" is the one to be recommended. All methods which depend upon chemical agents must be looked upon in a critical manner. Numerous ones are in every day use which a careful bacteriological test would condemn, and no surgeon should accept any method of sterilization, however much it has to recommend it in its simplicity, unless it is above criticism from a bacteriological standpoint.

Date. 1899.	Bacteria.	Time of sterilization.	Results.
May 24th.....	A. S. M.	30 mins.	Sterile.
" 25th.....	"	30 "	"
" 26th.....	"	30 "	"
" 27th.....	"	25 "	"
June 1st.....	"	15 "	"
" 9th.....	"	25 "	"
" 12th.....	"	20 "	"
" 20th.....	"	15 "	"
" 22nd	"	10 "	"
" 23rd.....	"	10 "	"
July 15th	"	10 "	"
" 20th	"	10 "	"

SUMMARIES OR TITLES OF PAPERS BY MEMBERS OF THE HOSPITAL AND MEDICAL SCHOOL STAFF APPEARING ELSEWHERE THAN IN THE BULLETIN.

JOHN M. T. FINNEY, M. D. Perforating Ulcer of the Stomach.—*Annals of Surgery*, July, 1900.

J. WHITRIDGE WILLIAMS, M. D. The Indications for the Employment of Cesarean Section, Symphyseotomy, and Craniotomy in Contracted Pelvis.—*Maryland Medical Journal*, July, 1900.

OTTO G. RAMSAY, M. D. A Case of Myoma of the Bladder.—*Phila. Medical Journal*, July 7 and July 14, 1900.

GEORGE W. DOBBIN, M. D. Ovariotomy in Schauta's Clinic.—*Maryland Medical Journal*, July, 1900.

HOWARD A. KELLY, M. D. An Improved Vesical Speculum.—*American Journal of Obstetrics*, June, 1900.

HUNTER ROBB, M. D. The Suppuration of the Wound after Abdominal Section, Based upon an Analysis of 114 Consecutive Unselected Abdominal Sections without a Death.—*Cleveland Journal of Medicine*, June, 1900.

JOHN G. CLARK, M. D. Historic and Practical Remarks on the Operative Treatment of Cancer of the Cervix.—*University Medical Magazine*, June, 1900.

BOOKS RECEIVED.

A Memoir of Henry Jacob Bigelow, A. M., M. D., LL. D. 1900. 8vo. 297 pages. Little, Brown and Company, Boston.

I. The Mechanism of Dislocations and Fracture of the Hip. II. Lithotapaxy, or Rapid Lithotrity with Evacuation. By Henry Jacob Bigelow, A. M., M. D., LL. D. 1900. 8vo. 356 pages. Little, Brown and Company, Boston.

Orthopedic Surgery and Other Medical Papers. By Henry Jacob Bigelow, A. M., M. D., LL. D. 1900. 8vo. 373 pages. Little, Brown and Company, Boston.

Surgical Anæsthesia, Addresses and Other Papers. By Henry Jacob Bigelow, A. M., M. D., LL. D. 1900. 8vo. 378 pages. Little, Brown and Company, Boston.

The Treatment of Fractures. By Charles Locke Scudder, M. D. Assisted by Frederic J. Cotton, M. D. With 585 Illustrations. 1900. 8vo. 433 pages. W. B. Saunders, Philadelphia.

University of Pennsylvania, Contributions from the William Pepper Laboratory of Clinical Medicine. 1900. 4to. 479 pages. Published on the Phoebe A. Hearst Foundation, Philadelphia.

Annual Report of the Department of Agriculture. For the fiscal year ended June 30, 1899. Report of the Secretary of Agriculture. Miscellaneous Reports. 1899. 8vo. LXX + 266 pages. Government Printing Office, Washington.

International Contributions to Medical Literature. "Festschrift" in Honor of Abraham Jacobi, M. D., LL. D., to Commemorate the Seventieth Anniversary of his Birth, May Sixth, 1900. 4to. XIII + 496 pages. 1900. The Knickerbocker Press, New York.

Contributions to the Science of Medicine. Dedicated by his pupils to William Henry Welch on the Twenty-fifth Anniversary of his Doctorate. 1900. 4to. 1066 pages. The Johns Hopkins Press, Baltimore.

PUBLICATIONS OF THE JOHNS HOPKINS HOSPITAL.

THE JOHNS HOPKINS HOSPITAL REPORTS.

VOLUME I. 423 pages, 99 plates.

Report in Pathology.

The Vessels and Walls of the Dog's Stomach; A Study of the Intestinal Contraction; Healing of Intestinal Sutures; Reversal of the Intestine; The Contraction of the V-na Portae and its Influence upon the Circulation. By F. P. MALL, M. D.

A Contribution to the Pathology of the Gelatinous Type of Cerebellar Sclerosis (Atrophy). By HENRY J. BERKLEY, M. D.

Reticulated Tissue and its Relation to the Connective Tissue Fibrils. By F. P. MALL, M. D.

Report in Dermatology.

Two Cases of Protozoan (Coccidioidal) Infection of the Skin and other Organs. By T. C. GILCHRIST, M. D., and EMMET RIXFORD, M. D.

A Case of Blastomycetic Dermatitis in Man; Comparisons of the Two Varieties of Protozoa, and the Blastomyces found in the preceding Cases, with the so-called Parasites found in Various Lesions of the Skin, etc.: Two Cases of Molluscum Fibrosum; The Pathology of a Case of Dermatitis Herpetiformis (Duhring). By T. C. GILCHRIST, M. D.

Report in Pathology.

An Experimental Study of the Thyroid Gland of Dogs, with especial consideration of Hypertrophy of this Gland. By W. S. HALSTED, M. D.

VOLUME II. 570 pages, with 28 plates and figures.

Report in Medicine.

On Fever of Hepatic Origin, particularly the Intermittent Pyrexia associated with Gallstones. By WILLIAM OSLER, M. D.

Some Remarks on Anomalies of the Uvula. By JOHN N. MACKENZIE, M. D.

On Pyrodin. By H. A. LAFLEUR, M. D.

Cases of Post-febrile Insanity. By WILLIAM OSLER, M. D.

Acute Tuberculosis in an Infant of Four Months. By HARRY TOULMIN, M. D.

Rare Forms of Cardiac Thrombi. By WILLIAM OSLER, M. D.

Notes on Endocarditis in Phthisis. By WILLIAM OSLER, M. D.

Report in Medicine.

Tubercular Peritonitis. By WILLIAM OSLER, M. D.

A Case of Raynaud's Disease. By H. M. THOMAS, M. D.

Acute Nephritis in Typhoid Fever. By WILLIAM OSLER, M. D.

Report in Gynecology.

The Gynecological Operating Room. By HOWARD A. KELLY, M. D.

The Laparotomies performed from October 16, 1889, to March 3, 1890. By HOWARD A. KELLY, M. D., and HUNTER ROBB, M. D.

The Report of the Autopsies in Two Cases Dying in the Gynecological Wards without Operation; Composite Temperature and Pulse Charts of Forty Cases of Abdominal Section. By HOWARD A. KELLY, M. D.

The Management of the Drainage Tube in Abdominal Section. By HUNTER ROBB, M. D.

The Gonococcus in Pyosalpinx; Tuberculosis of the Fallopian Tubes and Peritoneum Ovarian Tumor; General Gynecological Operations from October 15, 1889, to March 4, 1890. By HOWARD A. KELLY, M. D.

Report of the Urinary Examination of Ninety-one Gynecological Cases. By HOWARD A. KELLY, M. D., and ALBERT A. GHRISKEY, M. D.

Ligature of the Trunks of the Uterine and Ovarian Arteries as a Means of Checking Hemorrhage from the Uterus, etc. By HOWARD A. KELLY, M. D.

Carcinoma of the Cervix Uteri in the Negress. By J. W. WILLIAMS, M. D.

Elephantiasis of the Clitoris. By HOWARD A. KELLY, M. D.

Myxo-Sarcoma of the Clitoris. By HUNTER ROBB, M. D.

Koipo-Ureterotomy. Incision of the Ureter through the Vagina, for the treatment of Ureteral Stricture; Record of Deaths following Gynecological Operations. By HOWARD A. KELLY, M. D.

Report in Surgery, I.

The Treatment of Wounds with Especial Reference to the Value of the Blood Clot in the Management of Dead Spaces. By W. S. HALSTED, M. D.

Report in Neurology, I.

A Case of Chorea Insaniens. By HENRY J. BERKLEY, M. D.

Acute Angio-Neurotic Oedema. By CHARLES E. SIMON, M. D.

Haematomyelia. By AUGUST HOCH, M. D.

A Case of Cerebro-Spinal Syphilis, with an unusual Lesion in the Spinal Cord. By HENRY M. THOMAS, M. D.

Report in Pathology, I.

Amœbic Dysentery. By WILLIAM T. COUNCILMAN, M. D., and HENRI A. LAFLEUR, M. D.

VOLUME III. 766 pages, with 69 plates and figures.

Report in Pathology.

Papillomatous Tumors of the Ovary. By J. WHITRIDGE WILLIAMS, M. D.

Tuberculosis of the Female Generative Organs. By J. WHITRIDGE WILLIAMS, M. D.

Report in Pathology.

Multiple Lympho-Sarcomata, with a report of Two Cases. By SIMON FLEXNER, M. D.

The Cerebellar Cortex of the Dog. By HENRY J. BERKLEY, M. D.

A Case of Chronic Nephritis in a Cow. By W. T. COUNCILMAN, M. D.

Bacteria in their Relation to Vegetable Tissue. By H. L. RUSSELL, PH. D.

Heart Hypertrophy. By WM. T. HOWARD, JR., M. D.

Report in Gynecology.

The Gynecological Operating Room; An External Direct Method of Measuring the Conjugata Vera; Prolapsus Uteri without Diverticulum and with Anterior Enterocele; Lipoma of the Labium Majus; Deviations of the Rectum and Sigmoid Flexure associated with Constipation a Source of Error in Gynecological Diagnosis; Operation for the Suspension of the Retroflexed Uterus. By HOWARD A. KELLY, M. D.

Potassium Permanganate and Oxalic Acid as Germicides against the Pyogenic Cocci. By MARY SHERWOOD, M. D.

Intestinal Worms as a Complication in Abdominal Surgery. By A. L. STAVELY, M. D.

Gynecological Operations not involving Cœliotomy. By HOWARD A. KELLY, M. D. Tabulated by A. L. STAVELY, M. D.

The Employment of an Artificial Retroposition of the Uterus in covering Extensive Denuded Areas about the Pelvic Floor; Some Sources of Hemorrhage in Abdominal Pelvic Operations. By HOWARD A. KELLY, M. D.

Photography applied to Surgery. By A. S. MURRAY.

Traumatic Atresia of the Vagina with Hæmatokolpos and Hæmatometra. By HOWARD A. KELLY, M. D.

Urinalysis in Gynecology. By W. W. RUSSELL, M. D.

The Importance of employing Anæsthesia in the Diagnosis of Intra-Pelvic Gynecological Conditions. By HUNTER ROBB, M. D.

Resuscitation in Chloroform Asphyxia. By HOWARD A. KELLY, M. D.

One Hundred Cases of Ovariotomy performed on Women over Seventy Years of Age. By HOWARD A. KELLY, M. D., and MARY SHERWOOD, M. D.

Abdominal Operations performed in the Gynecological Department, from March 5, 1890, to December 17, 1892. By HOWARD A. KELLY, M. D.

Record of Deaths occurring in the Gynecological Department from June 6, 1890, to May 4, 1892.

VOLUME IV. 504 pages, 33 charts and illustrations.

Report on Typhoid Fever.

By WILLIAM OSLER, M. D., with additional papers by W. S. THAYER, M. D., and J. HEWETSON, M. D.

Report in Neurology.

Dementia Paralytica in the Negro Race; Studies in the Histology of the Liver; The Intrinsic Pulmonary Nerves in Mammalia; The Intrinsic Nerve Supply of the Cardiac Ventricles in Certain Vertebrates; The Intrinsic Nerves of the Submaxillary Gland of *Mus musculus*; The Intrinsic Nerves of the Thyroid Gland of the Dog; The Nerve Elements of the Pituitary Gland. By HENRY J. BERKLEY, M. D.

Report in Surgery.

The Results of Operations for the Cure of Cancer of the Breast, from June, 1889, to January, 1894. By W. S. HALSTED, M. D.

Report in Gynecology.

Hydrosalpinx, with a report of twenty-seven cases; Post-Operative Septic Peritonitis; Tuberculosis of the Endometrium. By T. S. CULLEN, M. B.

Report in Pathology.

Deciduoma Malignum. By J. WHITRIDGE WILLIAMS, M. D.

VOLUME V. 480 pages, with 32 charts and illustrations.

CONTENTS:

The Malarial Fevers of Baltimore. By W. S. THAYER, M. D., and J. HEWETSON, M. D.

A Study of some Fatal Cases of Malaria. By LEWELLYS F. BARKER, M. B.

Studies in Typhoid Fever.

By WILLIAM OSLER, M. D., with additional papers by G. BLUMER, M. D., SIMON FLEXNER, M. D., WALTER REED, M. D., and H. C. PARSONS, M. D.

VOLUME VI. 414 pages, with 79 plates and figures.

Report in Neurology.

Studies on the Lesions produced by the Action of Certain Poisons on the Cortical Nerve Cell (Studies Nos. I to V). By HENRY J. BERKLEY, M. D.

Introductory.—Recent Literature on the Pathology of Diseases of the Brain by the Chromate of Silver Methods; Part I.—Alcohol Poisoning.—Experimental Lesions produced by Chronic Alcoholic Poisoning (Ethyl Alcohol). 2. Experimental Lesions produced by Acute Alcoholic Poisoning (Ethyl Alcohol); Part II.—Serum Poisoning.—Experimental Lesions induced by the Action of the Dog's Serum on the Cortical Nerve Cell; Part III.—Ricin Poisoning.—Experimental Lesions induced by Acute Ricin Poisoning. 2. Experimental Lesions induced by Chronic Ricin Poisoning; Part IV.—Hydrophobic Toxæmia.—Lesions of the Cortical Nerve Cell produced by the Toxine of Experimental Rabies; Part V.—Pathological Alterations in the Nuclei and Nucleoli of Nerve Cells from the Effects of Alcohol and Ricin Intoxication; Nerve Fibre Terminal Apparatus; Asthenic Bulbar Paralysis. By HENRY J. BERKLEY, M. D.

Report in Pathology.

Fatal Puerperal Sepsis due to the Introduction of an Elm Tent. By THOMAS S. CULLEN, M. B.

Pregnancy in a Rudimentary Uterine Horn. Rupture, Death, Probable Migration of Ovum and Spermatozoa. By THOMAS S. CULLEN., M. B., and G. L. WILKINS, M. D.

Adeno-Myoma Uteri Diffusum Benignum. By THOMAS S. CULLEN, M. B.

A Bacteriological and Anatomical Study of the Summer Diarrhœas of Infants. By WILLIAM D. BOOKER, M. D.

The Pathology of Toxalbumin Intoxications. By SIMON FLEXNER, M. D.

VOLUME VII. 537 pages with illustrations.

I. A Critical Review of Seventeen Hundred Cases of Abdominal Section from the standpoint of Intra-peritoneal Drainage. By J. G. CLARK, M. D.

II. The Etiology and Structure of true Vaginal Cysts. By JAMES ERNEST STOKES, M. D.

III. A Review of the Pathology of Superficial Burns, with a Contribution to our Knowledge of the Pathological Changes in the Organs in cases of rapidly fatal burns. By CHARLES RUSSELL BARDEEN, M. D.

IV. The Origin, Growth and Fate of the Corpus Luteum. By J. G. CLARK, M. D.

V. The Results of Operations for the Cure of Inguinal Hernia. By JOSEPH C. BLOODGOOD, M. D.

VOLUME VIII. About 500 pages with illustrations. (In press.)

On the role of Insects, Arachnids, and Myriapods as carriers in the spread of Bacterial and Parasitic Diseases of Man and Animals. By GEORGE H. F. NUTTALL, M. D., PH. D.

Studies in Typhoid Fever.

By WILLIAM OSLER, M. D., with additional papers by J. M. T. FINNEY, M. D., S. FLEXNER, M. D., I. P. LYON, M. D., L. P. HAMBURGER, M. D., H. W. CUSHING, M. D., J. F. MITCHELL, M. D., C. N. B. CAMAC, M. D., N. B. GWYN, M. D., CHARLES P. EMERSON, M. D., H. H. YOUNG, M. D., and W. S. THAYER, M. D.

The price of a set bound in cloth (Vols. I-VII) of the Hospital Reports is $35.00. Vols. I, II and III are not sold separately. The price of Vols. IV, V, VI and VII is $5.00 each.

Subscriptions for the above publications may be sent to

THE JOHNS HOPKINS PRESS, BALTIMORE, MD.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by THE FRIEDENWALD CO., Baltimore. Single copies may be procured from Messrs. CUSHING & CO. and the BALTIMORE NEWS CO., Baltimore. Subscriptions, $1.00 a year, may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifteen cents each.